



Kala Pohl. *Kona Coffee for 2*. Acrylic on canvas, 18" × 24".

This review of a single-institution experience in treating metastatic melanoma examines the utility of different treatments and suggests guidelines for interpreting survival and disease-free survival in clinical trials.

Overall and Progression-Free Survival in Metastatic Melanoma: Analysis of a Single-Institution Database

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Background: Many new agents are currently in trial in melanoma. It remains unclear, however, what the benefit of a given therapy may be since information on progression-free and overall survival of untreated patients is limited. Since few trials in melanoma have had a non-treated cohort, it remains unclear what survival can be expected in patients who are not treated with chemotherapy.

Methods: To help develop parameters for future trials, we analyzed treatment history and survival in 212 patients with metastatic melanoma seen at our institution between January 1998 and September 2003. A retrospective analysis was done using a database created for melanoma patients at our center. Patient survival information was determined from this database, tumor registry, Social Security index, and direct patient calls. Patient staging information was determined according to the 2001 guidelines. Non-chemotherapy-treated patients with M1c disease were used as "controls."

Results: The median survival of stage M1c melanoma was 6.0 months. Survival was longer for stage M1a and M1b and shorter in older patients. No significant differences were found in survival based on gender. Among chemotherapy-treated patients, those with progressive disease on treatment or with increased lactate dehydrogenase (LDH) fared worse than those with a clinical response or normal LDH, respectively. Patients treated with either biochemotherapy or temozolomide and thalidomide survived longer than those who received no chemotherapy treatment. Dacarbazine (DTIC) treatment did not prolong survival.

Conclusions: In this retrospective review of patients treated at a single institution, those treated with multiagent chemotherapy but not with single-agent DTIC appeared to have had a survival benefit.

Introduction

The incidence of malignant melanoma has risen every year in the last 3 decades. In 2006, an estimated 6,900 deaths in the United States will be due to metastatic melanoma.¹ The prognosis is poor: the 5-year survival rate of patients with visceral involvement is under 10%.² Chemotherapy for metastatic melanoma is only modestly effective. The most commonly used chemotherapy agent in melanoma is dacarbazine (DTIC),³ which gives a 10% to 20% response rate. Although this drug has been in clinical use for 30 years, it is still not clear if it improves survival; no progressive, randomized trial has compared DTIC to observation and it is unlikely that such a trial will ever be done. The cytokine interleukin-2 (IL-2) also has activity in melanoma,^{4,5} although its survival advantage over observation-only management is also unknown. In a randomized phase III trial, combination chemotherapy improved response rates but not survival compared with DTIC alone.⁶ More recently, "biochemotherapy" regimens that include IL-2 and interferon α -2b in addition to multiagent chemotherapy have been developed.⁷ However, when compared in randomized trials to a multiagent chemotherapy regimen, they did not show an improvement in survival.^{8,9} Another agent that has been introduced in metastatic melanoma is temozolomide, an oral alkylating agent.^{10,12} The combination of temozolomide and thalidomide^{13,14} appears active in melanoma, although its impact on survival is unclear. Recently, the combination of oblimersen (antisense oligonucleotide to bcl-2) and DTIC was compared to DTIC alone. No advantage in survival was found with this combination, although an improvement in response rates to the combination arm was observed.¹⁵

Several questions regarding the design of melanoma trials are unlikely to be answered by prospective clinical trials but are important in assessing the value of a novel therapy. One question is whether single-agent or multiagent chemotherapy treatment is

associated with any survival advantage over no therapy. Another important issue is determining parameters for a successful phase II or phase III trial, especially if a novel signaling agent or immunotherapeutic drug might not produce many objective responses.

Patients and Methods

Melanoma Database

In an attempt to address the issues described above, we conducted an analysis of patient outcomes using the melanoma database at our center. Patient records in this database with the diagnosis of stage IV melanoma were analyzed by comparing outcomes based on treatment modalities. The melanoma database was initiated in 1985. It is a custom database constructed with Clarion for Windows 5.5 Enterprise Edition (Soft Velocity, Inc). The database currently contains over 8,500 patient records and implements 19 discrete elements for each patient, including initial diagnosis, pathology, sentinel node status, clinical history, clinical examination, medications, surgery, radiation, chemotherapy, immunotherapy, limb perfusion, staging, recurrence, and follow-up. The database can be searched for specific entries under each discrete category. It is fully encrypted and password protected.

Patient Population

All patients with pathologically proven stage IV melanoma entered in the database were included in this analysis. Patient charts and electronic records were reviewed for each case. Criteria for selection included recent follow-up records (within the last 12 months) or a known date of death. The analysis included patients with their initial visit from January 1998 to September 2003. Patients were stratified into five groups based on treatment regimens:

- Group 1: no treatment (n = 70)
- Group 2: treatment with DTIC (n = 45)
- Group 3: treatment with multiagent DTIC regimen (n = 19)
- Group 4: treatment with a combination of DTIC, cisplatin, vinblastine, IL-2, and interferon α -2b (biochemotherapy) (n = 57)
- Group 5: treatment with temozolomide and thalidomide (n = 21)

The untreated patients extracted from the melanoma database were all stage IV M1c. Exclusion criteria for untreated patients included chemotherapy or IL-2 treatment but they may have received experimental vaccines and/or surgery. Patients who had an elevated LDH at any time prior to treatment higher than the upper limit of normal at our institution were considered to have an elevated LDH. The date of death was retrieved from the Tumor Registry at our institution and

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Abbreviations used in this paper: LDH = lactate dehydrogenase, DTIC = dacarbazine, IL-2 = interleukin-2, ECOG = Eastern Cooperative Oncology Group, CI = confidence interval.

the Social Security Death Index and was verified with family members. The Moffitt Cancer Center Scientific Research Committee and the Institutional Review Board at the University of South Florida approved this study.

Treatment Regimens

We selected for review only patients with completely documented treatment histories. Those who were untreated could not have received any chemotherapy or high-dose IL-2 but could have received surgery or could have received vaccine therapy on clinical trials. Patients treated with DTIC had received at least 1 cycle of DTIC given at any dose over any schedule but without the addition of other chemotherapy. Patients who received biochemotherapy received concurrent biochemotherapy administered in a decrescendo fashion¹⁶ or according to the ECOG 3695 trial by the Eastern Cooperative Oncology Group.¹¹ Patients receiving temozolomide and thalidomide were given treatment that was modified from Hwu et al.^{13,14,17} They received 75 mg/m² per day of temozolomide for 3 weeks on and 1 week off, with 200 mg/day of thalidomide given continuously. Patients in the untreated group received no chemotherapy or IL-2 but could have received experimental vaccine therapy or surgery or radiation. All untreated patients and those treated with temozolomide and thalidomide had stage M1c disease, but patients with biochemotherapy or DTIC could have had either M1a, M1b, or M1c disease. Only patients with complete treatment histories, pathologically documented melanoma, and follow-up within

the last 12 months or known date of death were included in this study. Patients who received any regimen that could not be classified as above were excluded from this study.

Statistical Methods

This study is a retrospective, single-institution analysis of patients with stage IV melanoma seen at our center. Patients were identified through the Melanoma Database described above and through chart review. The primary goal of this analysis was to study the survival of patients who received different treatment modalities. Patient characteristics were recorded on Excel spreadsheets and analyzed with the SPSS version 12 statistical software (SPSS Inc, Chicago, Ill). The Kaplan-Meier statistical method was used to generate time to progression and survival curves. The survival curves were compared using the Mantel-Haenszel log-rank test. All confidence limits are 95% intervals. In order to study the influence of multiple prognostic factors in this analysis, we used a multivariate Cox proportional hazard model to calculate the hazard ratios of treatment modalities.

Results

Patient Demographics

A total of 768 patients with stage IV melanoma presented to the Cutaneous Oncology clinic at our institution between January 1998 and September 2003. Com-

Table 1. — Demographic Characteristics of Patients Reviewed

	Untreated (n = 70) (Group 1)	DTIC (n = 45) (Group 2)	Multiagent DTIC Regimen (n = 19) (Group 3)	Biochemotherapy (n = 57) (Group 4)	Temozolomide and Thalidomide (n = 21) (Group 5)
Median Age (yrs)	64	66	52	46	46
Sex					
Men	46	34	14	41	13
Women	24	11	5	16	8
Primary Site					
Skin	68	39	17	41	20
Ocular	2	1	1	3	0
Mucosal	0	1	1	3	0
Unknown	0	4	0	10	1
Stage					
M1a	0	5	0	8	0
M1b	0	16	8	8	0
M1c	70	24	11	41	21
Adjuvant Therapy					
Interferon	0	14	0	13	2
Vaccine	4	2	2	3	0
GM-CSF	0	2	0	2	0
IFN + Vaccine	0	0	0	3	0
Prior Chemotherapy					
1 regimen	0	7	4	12	4
2 regimens	0	0	0	0	0
3 regimens	0	0	0	0	0

plete treatment records and staging studies were recorded on 212 patients. Of these, 142 patients were treated with a chemotherapy regimen; the remaining 70 patients were not treated with either chemotherapy or IL-2 but had M1c disease. Patients were included in this study based to our ability to assign them to one of the five treatment groups and on the availability of complete records for assignment of prognostic factors. Patient characteristics are summarized in Table 1.

Age and Gender

Age was considered a discontinuous variable and was divided into three arbitrary groups: 21 to 40 years, 41 to 60 years, and 61 years and above. Ninety-one patients were age 61 and above, 78 patients were age 41 to 60, and 43 patients were age 21 to 40. The age groups differed significantly with respect to survival ($P = .0033$), with median survival times of 5.0 months (95% confidence interval [CI] 4.0–6.0) for patients 61 years of age and older. Patients 21 to 40 years had a median survival of 7 months (95% CI 4.0–9.0 months),

and those between 41 and 60 years had a median survival of 8 months (95% CI 6.0–9.0 months). Kaplan-Meier survival curves of all three groups are shown in Fig 1. Gender was examined by log-rank test comparison of survival curves. Men had a median survival of 6 months (95% CI 5.0–8.0 months), and women had a median survival of 7 months (95% CI 5.0–8.0 months). No significant differences were seen ($P = .746$). Kaplan-Meier survival curves for men and women are shown in Fig 2.

Disease Stage

The American Joint Committee on Cancer (AJCC) 2001 classification proposed by Balch et al² mandates the allocation of patients with metastatic melanoma into three groups: (1) M1a with skin, subcutaneous, and lymph node disease, (2) M1b with lung metastasis, and (3) M1c with visceral metastasis or elevated lactate dehydrogenase (LDH) level. In our group of patients, those with M1c disease ($n = 167$) did worse, with a median survival of 6.0 months (95% CI 4.0–7.0

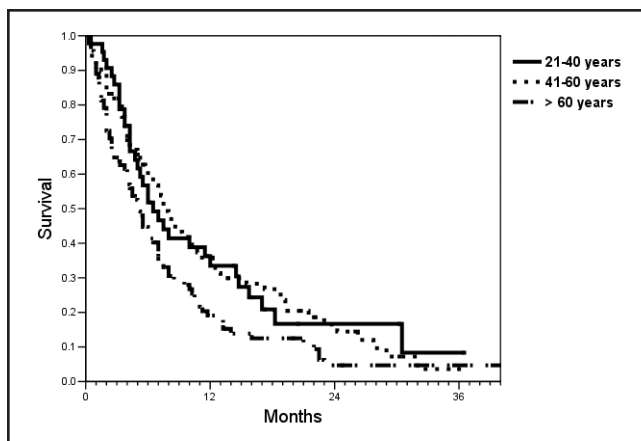


Fig 1. — Kaplan-Meier curves showing overall survival of patients of different ages with metastatic melanoma. Solid line = ages 21–40 ($n = 43$), dotted line = ages 41–60 ($n = 78$), and dashed line = ages 61 and above ($n = 91$).

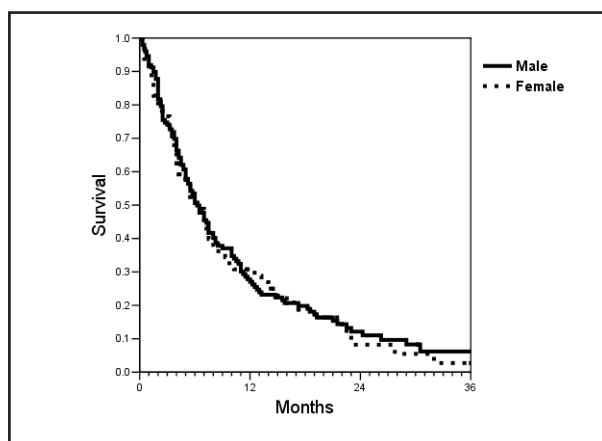


Fig 2. — Kaplan-Meier curves showing overall survival of patients separated by gender. Solid line = men ($n = 148$) and dotted line = women ($n = 64$).

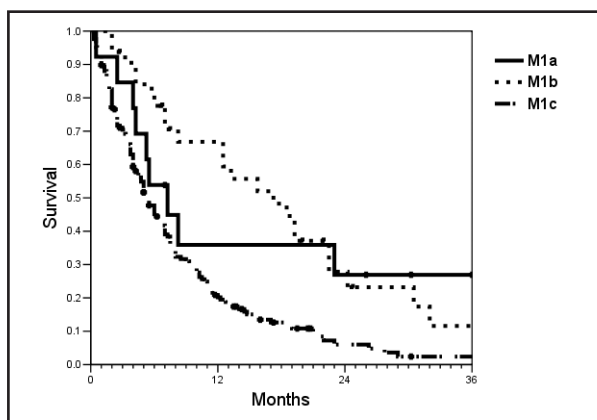


Fig 3. — Kaplan-Meier curves showing overall survival of patients distributed by stage. There was significant difference among these groups ($P = .0002$). Solid line = patients with M1a disease, dotted line = M1b disease, and dashed line = M1c disease.

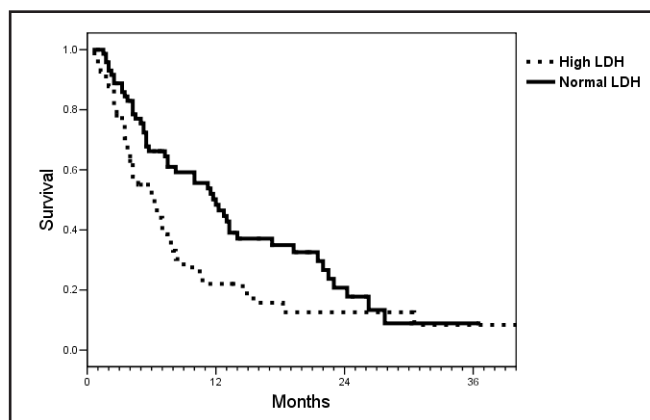


Fig 4. — Kaplan-Meier curves showing overall survival of patients compared by normal (solid line) or elevated LDH (dotted line) ($P = .0154$).

Table 2. — Survival and Response Data by Treatment Group

Treatment	Median Survival in Months (95% CI)	Response			
		Complete Response	Partial Response	Stable Disease	Progressive Disease
Untreated	4.0 (CI 2.2–5.8)	N/A	N/A	N/A	N/A
DTIC	6.0 (CI 3.65–8.35)	1 (2%)	2 (4%)	6 (13%)	36 (80%)
Multiagent DTIC Regimen	10.0 (CI 4–16)	1 (5%)	2 (10%)	4 (20%)	12 (64%)
Biochemotherapy	10.0 (CI 5.91–14.09)	3 (5%)	7 (12%)	14 (24%)	33 (59%)
Temozolomide and thalidomide	13.25 (CI .001–27.84)	1 (5%)	1 (5%)	7 (35%)	12 (60%)

N/A = not available

months), while those with M1a disease (n = 13) had a median survival of 7 months (95% CI 4.0–10 months) and, somewhat surprisingly, those with M1b (n = 32) had a median survival of 17 months (95% CI 9.0–26 months) ($\chi^2 = 19.676, P = .0003, df = 2$). These results are shown in Fig 3. It has also been recognized in the AJCC classification that patients with LDH levels greater than normal have a worse prognosis than those with a normal LDH level. We examined the effect of LDH on patients who had received either of the chemotherapy treatments. Patients with a normal LDH level survived almost twice as long (median survival, 12.0 months, [95% CI 8.85–15.15]) compared to those with an elevated LDH level (median survival 6.0 months, [95% CI 3.51–8.49]); these were significantly different by the log-rank test ($\chi^2 = 5.88, P = .0154$). This effect is illustrated in Fig 4.

Treatment Effects

We compared five groups of patients — group 1 received no chemotherapy treatment, group 2 received treatment with DTIC alone for at least 1 cycle, group 3 received treatment with any multiagent DTIC regimen, group 4 had treatment with concurrent biochemotherapy as described in the Methods section, and group 5 had treatment with temozolomide and thalidomide. The median survival and confidence interval for each

group are shown in Table 2, and Kaplan-Meier curves are shown in Fig 5. These results were compared by the log-rank test and were significantly different ($P = .0001$). The significance of the treatment effect was analyzed by examining the difference in survival of responders (complete response, partial response, or stable disease). These results are shown in Fig 6. Since there could be some confounding of these results due to an imbalance in prognostic factors such as age and stage, the treatment groups were also analyzed by the Cox proportional hazards method. This analysis is shown in Table 3. Age and gender did not increase hazard ratio in this multivariate analysis. Disease stage did reduce the hazard; the hazard ratio (relative to M1c) was 0.576 for stage M1a and 0.362 for stage M1b). Interestingly, all treatment modalities studied in this analysis were associated with a reduced hazard ratio when compared with group 1, the untreated group. The hazard ratio for DTIC (group 2) was 0.801 ($P = .342$), for multiagent DTIC regimen (group 3) was 0.596 ($P = .078$), for biochemotherapy (group 4) was 0.407 ($P = .001$), and for temozolomide and thalidomide (group 5) was 0.346 ($P = .001$).

To negate the influence of disease stage on outcome, we compared only patients with M1c disease who were treated with either different regimens or observation alone. The results of this analysis are

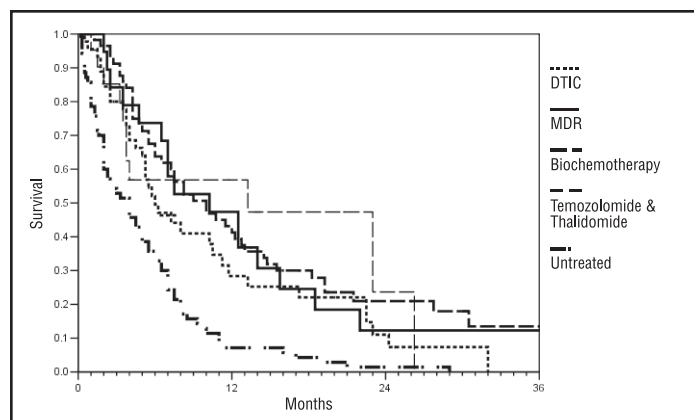


Fig 5. — Kaplan-Meier curves showing overall survival of patients compared by treatment group. Dotted line = DTIC (n = 45), solid line = multiagent DTIC regimen (n = 19), thick dashed line = biochemotherapy (n = 57), thin dashed line = temozolomide and thalidomide (n = 21), and dotted dashed line = untreated (n = 70). Log-rank test, $P = .0001$.

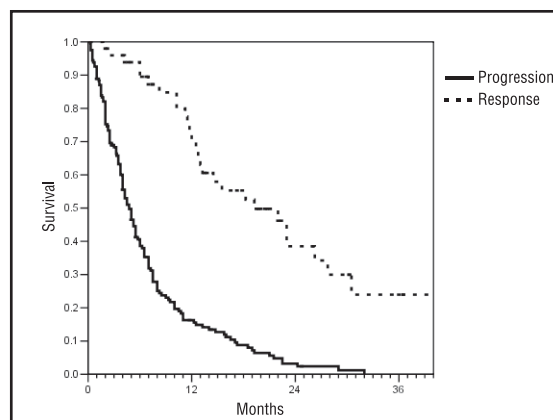


Fig 6. — Kaplan-Meier curves showing the differences in survival between patients with progressive disease (solid line) and patients with a response to treatment (dotted line). Log-rank test, $P = .0001$.

Table 3. — Cox Regression Analysis of Prognostic/Predictive Variables

Characteristic	Hazard Ratio	P	95% CI
Age (21–40 yrs)	0.990	0.968	0.614–1.596
Age (41–60 yrs)	0.918	0.641	0.640–1.316
Age (61 yrs and above)	—	—	—
Gender	0.989	0.990	0.698–1.363
M1a	0.576	0.140	0.277–1.198
M1b	0.362	0.001	0.213–0.615
M1c	—	—	—
DTIC	0.801	0.342	0.508–1.265
Multiagent DTIC Regimen	0.596	0.078	0.335–1.061
Biochemotherapy	0.407	0.001	0.261–0.633
Temozolomide + thalidomide	0.346	0.001	0.181–0.663
Untreated	—	—	—

shown in Fig 7. In this poor-risk patient population, treatment with either regimen was associated with a better outcome than no chemotherapy treatment. To confirm the treatment effect, we separated patients with progressive disease from those who had either stable disease, complete response, or partial response to treatment. A marked treatment effect was seen in terms of survival (Fig 8), suggesting that the differences seen in treatment groups may be due to treatment effects rather than patient selection. Since the temozolomide and thalidomide regimen has recently been shown to have impressive response rates,¹³ we compared survival with this regimen to survival with DTIC. Controlling for stage (all patients were M1c) still resulted in an impressive improvement in survival ($P = .01$).

Discussion

Historically, metastatic melanoma has been considered a chemotherapy-insensitive disease.¹⁸ Even though DTIC was approved by the US Food and Drug Adminis-

tration for use in melanoma over 2 decades ago, it is still not clear if this drug improves survival.⁵ Recent prospective, randomized studies have shown that the Dartmouth regimen (ie, combination chemotherapy with DTIC, carmustine, cisplatin, and tamoxifen) did not improve survival over DTIC alone⁶ and that biochemotherapy (cisplatin, vinblastine, DTIC, interferon, and IL-2) did not improve survival over combination chemotherapy (cisplatin, vinblastine, and DTIC).⁹ However, DTIC has not been compared directly to biochemotherapy, and neither has been compared to observation alone and is not likely to be compared in the future. Additionally, given the small size of most melanoma studies, it is not clear if a small magnitude of difference could be detected.

These issues affect decision making in the clinic for physicians as well as patients. Therefore, using the Melanoma Database, as described in the Patients and Methods section above, we analyzed more than 6,900 unique patients with melanoma who were treated at our center since 1985. We identified 749 patients with stage IV disease. Further study of these records led us to narrow our review to 212 patients who had complete records and who could be classified into one of the five groups according to treatment regimen: group 1, no chemotherapy or IL-2 but could have been treated on experimental vaccine trials; group 2, single-agent DTIC; group 3, any multiagent DTIC regimen; group 4, concurrent biochemotherapy on one of two similar regimens^{9,15}; and group 5, the recently described temozolomide and thalidomide regimen^{17,19} modified as noted in the Methods section. Since all patients in group 5 and most patients in group 4 had M1c disease, we chose untreated patients with M1c disease in order to assemble a more comparable group. This also excluded the effect of surgical resection and isolated limb perfusion (both of which are commonly

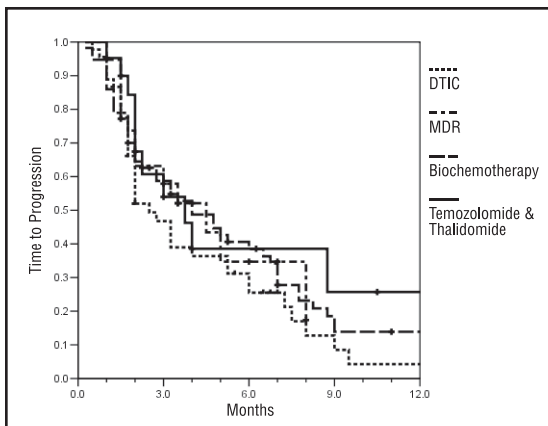


Fig 7. — Kaplan-Meier curves showing time to progression of disease compared by treatment group. The time to progression curves are shown for patients treated with DTIC (n = 45, dotted line), multiagent DTIC regimen (n = 19, close dotted line), and biochemotherapy (n = 57, wide dotted line), and temozolomide and thalidomide (n = 21, solid line). Log-rank test, $P = .4770$.

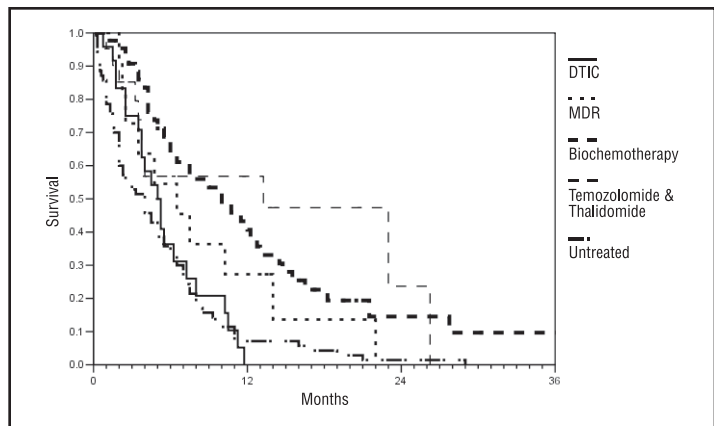


Fig 8. — Kaplan-Meier curves showing survival of M1c stage patients compared by treatment group. The survival curves are shown for patients treated with DTIC (n = 24, solid line), multiagent DTIC regimen (n = 11, thin dotted line), biochemotherapy (n = 43, thick dotted line), temozolomide and thalidomide (n = 21, thin dashed line), and observation (n = 70, dotted dashed line). Log-rank test, $P = .0001$.

employed in stage M1a and M1b) that can make it difficult to compare treatment effects.

We employed two types of statistical analyses in this study. All prognostic factors were compared by Kaplan-Meier analysis and the log-rank test. Furthermore, we compared treatment effects in a multivariate model using the Cox regression analysis to estimate hazard ratios. Finally, we compared only those patients with M1c disease in different treatment groups.

Gender was not a significant prognostic factor in this data set. Age was significant in log-rank analysis, with patients older than 60 years of age faring worse than those age 21–40 or 41–60, but age was not a significant factor in multivariate Cox regression analysis. Stage was a powerful prognostic factor, with stage M1c being associated with significantly higher risk of death compared with stage M1a or M1b with either log-rank or Cox analysis. Increased LDH was similarly strongly associated with increased risk of death. Disease bulk did not significantly increase risk (data not shown). Finally, we compared patients across treatment groups. Since stage influences prognosis, we also compared stage M1c patients across these groups. We found that treatment with single-agent DTIC, multiagent DTIC regimen, biochemotherapy, and the newer temozolomide and thalidomide regimen were all superior to observation alone by log-rank analysis (Table 2 and Fig 5). The median survival with biochemotherapy and with temozolomide plus thalidomide was impressively higher in this analysis. Since several factors other than treatment history could account for these findings, we also examined these data with a Cox regression model. With this model, DTIC treatment had a hazard ratio of death of 0.801 but this effect was not statistically significant ($P = .342$). The hazard ratio with multiagent DTIC regimens was 0.596 ($P = .078$) while biochemotherapy had a hazard ratio of 0.407 ($P = .001$), and temozolomide and thalidomide treatment had a hazard ratio of 0.346 ($P = .001$). Furthermore, we compared patients with M1c disease treated with either DTIC or temozolomide and thalidomide. A significant ($P = .01$) difference was found and better survival seen in patients treated with the combination regimen.

Several caveats should be emphasized in this study. Since no information on performance status or weight loss pretreatment was collected, these factors may have confounded results. A previous study looking at the ECOG experience has shown a significant impact of performance status on survival.²⁰ However, since most of these treatment regimens do not mandate a good performance status, we do not believe these results are associated with a performance status effect. Any single institution study also inherently incorporates a referral bias. Physician bias may also have played a role in offering the multiagent chemotherapy regimens only to patients with a better likelihood of survival. While a chart review

of the untreated patients does not suggest that this was the case (patients were often on vaccine trials that mandate an excellent performance status), only a prospective, randomized study can answer this question.

Finally, this study raises some questions about future trials. It may be reasonable to prospectively evaluate a multiagent chemotherapy regimen compared with best supportive care in order to unambiguously establish the survival benefit of alkylating agent-based chemotherapy in melanoma. Our results suggest that DTIC alone has only a modest survival benefit but that multiagent regimens may have a survival benefit in melanoma when compared to observation.

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