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Phase II evaluation of dibromodulcitol and actinomycin D, hydroxyurea, and cyclophosphamide in previously untreated patients with malignant melanoma

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Abstract

In this Eastern Cooperative Oncology Group (ECOG) phase II study, dibromodulcitol (DBD) and a combination of actinomycin D, hydroxyurea, and cyclophosphamide (AHC) were compared with methyl-CCNU, the current ECOG standard, in patients who had received no prior chemotherapy for disseminated malignant melanoma. The response rates were 6% (3/50) for AHC, 9% (3/34) for DBD, and 14% (7/49) for methyl-CCNU. Median survival times were 4, 5, and 6 months, respectively. Neither regimen appears to offer any advantage over methyl-CCNU as front-line therapy for patients with disseminated melanoma.

Introduction

There are currently few agents with activity against disseminated malignant melanoma. DTIC and the nitrosoureas have modest antitumor activity, but the remissions are brief and survival is limited [1–7]. Combinations of these agents do not improve results substantially [3]. To identify new agents and combinations, the Eastern Cooperative Oncology Group (ECOG) developed a phase II master protocol, EST 1675, which allowed for simultaneous testing of up to three new regimens in comparison with a control arm. The study was multigenerational; new arms were activated to replace arms which had completed accrual. Methyl-CCNU was the control agent, based on a prior ECOG study. [8]. The third generation of the study was reported previously [9]. This paper presents the results of the second and fourth generations.

Actinomycin D, cyclophosphamide, and hydroxyurea have produced responses as single agents in malignant melanoma [10]. In the comprehensive review of Livingston and Carter [10], they were among the most active single agents against melanoma. Their use in combination in this study was based on a preliminary trial in which 3 responses were seen among 15 patients who had failed a combination of BCNU, DTIC, and Vincristine (H. Bruckner and S. Cohen, unpublished data).

Dibromodulcitol (NCS-104800, DBD) is an orally administered, myelotoxic, halogenated sugar alcohol which is thought to act as an alkylating agent [11,12]. Cross-resistance to other alkylating agents appears incomplete, suggesting that DBD may be useful in second-line therapy after treatment with regimens containing an alkylating agent [12]. Also of potential importance is DBD's lipid solubility and penetration into the central nervous system [13].

Phase I and II studies demonstrated potential antitumor activity against disseminated melanoma [14–19]. One study resulted in 3 complete and 2 partial responses among 25 patients with disseminated melanoma refractory to DTIC and a nitrosourea [17]. Another study had 2 complete and 2 partial responses among 43 patients, 25 of whom had prior chemotherapy, 23 with DTIC [19]. Interestingly, all responses occurred in patients with previous DTIC. Because responses are rare in previously treated patients [8], and because these response rates are comparable to that of DTIC and the nitrosoureas in previously untreated patients [11], further study of this agent in melanoma seemed warranted.

Materials and methods

The study was open to patients with histologically confirmed, surgically incurable melanoma. All had measurable disease and ECOG performance status 0–3. Patients with CNS metastases or who had received prior chemotherapy for recurrent or metastatic disease were ineligible. Patients who had received chemotherapy only as an adjuvant, however, were eligible provided they were not treated with one of the current study agents. Patients had to have recovered from the effects of previous chemotherapy, major surgery, or wide-field radiation therapy and had to be free of significant infection. Four weeks should have elapsed from cessation of prior chemotherapy unless it could be demonstrated that the patient had completely recovered from previous myelosuppression. Prior radiotherapy to measurable lesions was not a cause for exclusion if there was evidence of measurable progressive disease and four weeks had elapsed since the termination of radiotherapy. Patients must have had BUN < 25 mg%, creatinine < 1.5 mg%, bilirubin < 2.0%, WBC $\geq 4{,}000/mm^3$, and platelets $\geq 100{,}000/mm^3$. Informed consent was required from all patients.

The study design allowed more than one new regimen to be evaluated at a time, with methyl-CCNU (the ECOG standard therapy) as a control arm. Patients were randomized among the open arms by telephoning a central randomization desk. The randomization was by permuted blocks for each stratum with dynamic balancing by institution [20]. Patients were stratified by performance status (ECOG 0 or 1 versus ECOG 2 or 3) and by the most clinically significant disease site: a) liver, b) disease of lungs, bone, or viscera other than liver, or c) soft tissue or nodal disease only. During part of Generation II, an unbalanced randomization scheme was in effect, in which fewer patients were allocated to the control arm.

The second generation of the study evaluated actinomycin-D 0.5 mg/M² IV days 1 and 2, hydroxyurea 1500 mg/M² p.o. days 1–5, and cyclophosphamide 300 mg/M² i.v. days 1 and 2, to be repeated every 21 days, hereafter referred to as AHC. The fourth generation studied dibromodulcitol (DBD) 100 mg/M² p.o. hs daily. The concurrent control patients for these two generations received either methyl-CCNU 250 mg/M² p.o. single dose on day 1 q 6 weeks or methyl-CCNU 150 mg/M² p.o. single dose on day 1 q 3 weeks, except for 4 patients who received 200 mg/M² q 6 weeks. The control regimen was changed during the course of the study, after results from the first generation became available. Thus, the particular control regimen was related to chronological time, and was not a matter of investigator choice.

Dose modifications were based on hematologic toxicity. For AHC and DBD, doses were to be reduced to 50% if WBC was 3,000–4,000 or platelets were 75,000–100,000. Therapy was to be withheld if WBC $< 3{,}000$ or platelets $< 75{,}000$. For the 3-week schedule of methyl-CCNU, doses were to be reduced by 50% if WBC was 3,500–4,500 or platelets were 75,000–100,000. Therapy was to be withheld if WBC $< 3{,}500$ or platelets $< 75{,}000$. For the 6-week schedule, the next dose was to be reduced by 25% if the WBC nadir was $< 2{,}000$ or the platelet nadir was $< 75{,}000$. Drug was to be withheld if WBC $< 4{,}000$ or platelets $< 100{,}000$ at the time of scheduled treatment. If no drug was given due to toxicity, therapy was to be resumed once these levels returned to normal. A dose reduction of 50% was allowed at the discretion of the principle investigator for severe, intractable vomiting and could be omitted following a phone call to the study

Table 1. Status of patients entered on EST 1675 generations II and IV

	Generation II		Generation IV		
Status	AHC	Control	DBD	Control	Total
Entered	53	19	42	36	150
cancelled	1	0	2	0	3[a]
ineligible	2	2	5	4	13[b]
no data	0	0	1	0	1
Evaluable	50	17	34	32	133

[a] Ineligible; No evident disease at randomization; Refused treatment.
[b] Prior chemotherapy for recurrent disease [8]; CNS disease [2]; Lymphoma; Carcinoma; No measurable disease.

chairman. If there was no hematologic toxicity during any period of four consecutive weeks of therapy (WBC $\geq$ 4,000 and platelets $\geq$ 100,000) the DBD dose was to be escalated to 130 mg/M^2. If no toxicity occurred in the succeeding four weeks, a second escalation to 160 mg/M^2 was to be performed. If toxicity occurred after dose escalation, the modifications described above were to be applied.

Standard ECOG response criteria were utilized [21].

The minimum treatment period was 6 weeks unless serious toxicity occurred. Patients who experienced disease progression were taken off study provided they had completed the minimum treatment period. Patients in complete remission for 2 years were to be followed with no further chemotherapy.

The study design called for a new therapy to receive further testing if it produced more responses than the control. A sample size of approximately 40 patients per arm was required to assure that there was little chance ($\leq$7%) of missing an active regimen ($\geq$30% response rate), assuming a 15% response rate for methyl-CCNU. In comparison, a regimen with a 15% response rate had only a 44% chance of receiving further testing.

Results

Fifty evaluable patients on AHC and 17 on methyl-CCNU were entered during Generation II (Table 1). Of the methyl-CCNU controls, 5 received 250 mg/M^2 q 6 weeks, 4 received 200 mg/M^2 q 6 weeks, and 8 received 150 mg/M^2 q 3 weeks. There were 34 evaluable DBD patients and 32 evaluable controls (all 150 mg/M^2 MeCCNU q 3 weeks) on Generation IV.

No major imbalances existed in the distribution of patient characteristics between the treatment groups. Sixty-four percent of the patients were males, 84% were ambulatory, and 88% had lost less than 5% of body weight in the previous 6 months. Age ranged from 18 to 85, with a median of 57 years. Half had lung metastases, 35% had subcutaneous metastases, and 30% had liver disease.

Reactions to treatment were primarily nausea/vomiting and hematologic toxicities. On AHC, there were 15 (30%) cases of severe, and 16 (32%) of moderate, nausea/vomiting. There was one lethal toxicity. An 80-year-old patient returned to the hospital on day 11 after one course of therapy (days one to five), with WBC $<$ 100 and platelets = 6,000, and died 12 hours later. There were 5 (10%) cases each of moderate and severe hematologic toxicity. On DBD, there were two (6%) life-threatening cases of thrombocytopenia (platelets $<$ 25,000). There was also 6 (18%) severe and 10 (29%) moderate hematologic toxicites. Seven (21%) patients had moderate nausea/vomiting, with no severe cases reported. On methyl-CCNU, there were 4 (8%) severe and 19 (39%) moderate episodes of nausea/vomiting. There was one life-threatening case of thrombocytopenia, and 6 (12%) cases each of moderate and severe hematologic toxicities.

Table 2. Dose escalation for DBD

Total cases	34
Not eligible for escalation	15
off-study by week 4	9
leukopenia or thrombocytopenia	6[a]
Eligibility for escalation could not be fully determined, but probable failure to escalate	5
Definitely eligible for escalation	14
escalation performed	13
per protocol	9
not per protocol	4
escalation not performed	1[b]

[a] Includes 2 responders.

[b] Patient had response concurrent with thrombocytopenia. Recovered from thrombocytopenia for 4 consecutive weeks, but dose was not escalated.

There were 3 (6%) partial responses to AHC, each lasting 5 to 6 weeks, and 3 (9%) to DBD, lasting 10, 14, and 24 weeks, respectively. By contrast, there were 4 (8%) complete and 3 (6%) partial responses to methyl-CCNU, for an overall response rate of 14 % (3/17 (18%) on Generation II and 4/32 (12%) on Generation IV). The durations of the complete responses were 4, 25, 66+, and 198+ weeks, while the partial responses lasted 11, 12, and 27 weeks, respectively. Upper 95% confidence bounds on the response rates are 15%, 21%, and 25% for AHC, DBD, and methyl-CCNU, respectively. Median survival times, estimated by the method of Kaplan and Meier [22], were 4, 5, and 6 months, respectively.

As noted in Section 2, the DBD arm called for dose escalation if no hematologic toxicity occurred during any period of 4 consecutive weeks. In evaluating the efficacy of DBD, then, it is important to determine whether dose escalations were carried out as specified. Table 2 shows the dose escalation information for DBD. Fifteen patients did not meet the criteria for dose escalation. In another 5 cases, eligibility for escalation could not be determined fully, due to missing blood counts, but it appears that there was failure to escalate in each case. In any event, not recording weekly blood counts was a violation of protocol guidelines. Of the 19 patients who were probably eligible for escalation, 13 (68%) had some form of escalation and only 9 (47%) had escalation as specified in the protocol. Thus, the compliance with dose escalation was not satisfactory.

Discussion

This study was designed to have a small chance (7%) of rejecting a regimen with a 30% response rate in previously untreated patients with advanced melanoma. The response rate to AHC in this trial was only 6% compared with 14% for MeCCNU. This response rate for MeCCNU is consistent with that seen in other generations of this study [9]. Because the upper 95% confidence bound on the response rate for AHC is only 15%, it appears that AHC is not active as a front-line therapy in these patients.

The response rate to DBD (9%) was also disappointing. The upper 95% confidence bound on the response rate is only 21%, which is well below the target of 30%. Although compliance with dose escalation on the DBD arm was not satisfactory, it is unlikely that this was sufficient to account for the low response rate. All the responses occurred in patients who had dose-limiting toxicity at 100 mg/M^2. That is, of the 13 patients who did have dose escalation, none responded. Nine of these patients did encounter dose-limiting toxicity after escalation; the other four progressed before such toxicities occurred. In the four cases in which escalation was not performed per protocol, three had dose-limiting toxicity after escalation. Thus, there is no evidence that failure to escalate was the cause of the low response rate. Even if we exclude the 5 patients who were apparently not escalated, the response rate is only 10%. Thus, we were not able to duplicate the promising results observed by Bellet *et al.* despite having used both the same initial dose and subsequent dose escalation to induce hematologic toxicity as they suggested [17].

We conclude that neither AHC nor DBD are active front-line regimens for patients with metastatic malignant melanoma.

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Notes

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