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Short report

Conventional dose melphalan is inactive in metastatic melanoma: results of an Eastern Cooperative Oncology Group Study (E1687)

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Despite reports that i.v. melphalan is active in the settings of conditioning regimens utilizing high-dose chemotherapy for autologous bone marrow transplantation and in isolated limb perfusion for the treatment of malignant melanoma, its activity at conventional doses has never been defined in this disease. We conducted a phase II study of conventional-dose i.v. melphalan (30 mg/m^2) in 17 patients with metastatic melanoma. All patients were previously untreated with chemotherapy with performance status 0, 1 or 2. Forty-seven cycles were given with a median of two cycles. One patient was not evaluable due to early death. There were no responses in the 16 patients, resulting in a 0% response rate (95% confidence interval = 0–17%). We conclude that conventional-dose melphalan by i.v. administration has no appreciable activity in patients with metastatic malignant melanoma. [© 1999 Lippincott Williams & Wilkins.]

Key words: Eastern Cooperative Oncology Group, melanoma, melphalan.

Introduction

Melphalan (L-phenylalanine-mustard) is a nitrogen mustard substituted with the amino acid phenylalanine. It was synthesized based on the concept that melanin-producing malignancies that actively use phenylalanine or tyrosine would selectively concentrate this drug.[1] Later investigations showed the L-isomer was twice as active as the D-enantiomer. Since that time the drug has been provided as the active, L-isomer. This compound has been useful as an oral agent and has proved active in several tumor types sensitive to alkylating agents. The activity of i.v. melphalan, however, in the treatment of melanoma remains to be adequately defined. It has mainly been used i.v. in the setting of bone marrow transplantation and in isolated limb perfusion studies.

Bone marrow transplant programs have used high doses of i.v. melphalan in their conditioning regimens and have reported a consistent response rate for patients with melanoma undergoing such transplantation. These studies, however, have generally been phase I studies and not specifically directed toward melanoma patients. Reports to date include an 81% response rate with 25% complete remission (CR) (melphalan 60–100 mg/m^2 in combination with DTIC) with lower doses (melphalan 30–40 mg/m^2) having a 27% response rate with 11% CR.[2] Others reported combination studies with few melanoma patients and response rates of 50–75%.[3–5]

Isolated limb perfusion has also played a role in the treatment of locally advanced melanoma. Numerous studies have been performed using this technique, with reports of up to a 78% response rate in large

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numbers of patients,[6-8] though randomized studies to date have not convincingly shown a survival benefit for this technique.[9,10] The EORTC study of 832 patients randomized to isolated limb perfusion plus hyperthermia versus wide excision, however, failed to demonstrate improved time to distant metastases or survival, though in-transit metastasis rate was decreased from 6.6 to 3.3%.[11]

Based on these considerations and the variable absorption leading to significant pharmacokinetic variability for the oral formulation,[12] we undertook to study conventional-dose melphalan administered i.v. in patients with metastatic and measurable malignant melanoma in the Eastern Cooperative Oncology Group (ECOG).

Methods

Patients with measurable, histologically documented metastatic, residual or recurrent malignant melanoma were eligible for this study. Patients had measurable disease by ECOG criteria and adequate organ function with white blood cells (WBC) $\geqslant 4000/mm^3$, platelets $\geqslant 100\ 000/mm^3$, hemoglobin $\geqslant 10.0$ g/dl, BUN $\leqslant 25$ mg/dl, bilirubin $\leqslant 2.0$ mg/dl and creatinine $\leqslant 1.5$ mg/dl. ECOG performance status was required to be 0, 1 or 2. All patients were required to be previously untreated with chemotherapy, though one prior biological therapy was permitted in this trial. Prior radiation was permitted if there was measurable disease outside the radiotherapy port and 2 weeks had passed since completion of radiation. All patients gave written informed consent as approved by Institutional Review Board of their institutions. Standard ECOG response criteria were used.[13]

Intravenous melphalan was provided by the Cancer Treatment Evaluation Program of the National Cancer Institute. The drug was administered at a dose of 30 mg/m^2 in 100 ml of 5% dextrose solution over 30 min. Dosing was repeated every 3 weeks with the following dose modifications for hematologic toxicity: in the event that WBC had not returned to $\geqslant 4000/mm^3$ or platelets $\geqslant 100\ 000/mm^3$ at 21 days, therapy was delayed until counts returned to that level. Additionally, dose modifications were based on hematologic nadirs of the white blood cell count, with 25% reduction for WBC nadir $< 2000/mm^3$ or for a platelet nadir between 100 000 and 75 000/mm^3. In the event of nadir counts of platelets $< 75\ 000/mm^3$ or WBC $< 2000/mm^3$, the dose was reduced by 50% in the next cycle. Also, in the event that creatinine increased by $\geqslant$ 2-fold compared to the baseline value, the melphalan dose would be decreased by 50%. In the event that the nadir counts were WBC $> 3500/mm^3$ and platelets $> 100\ 000/mm^3$, the next dose would be given at a 25% escalation.

Patients were to be treated until complete remission plus two cycles or progression according to ECOG criteria. All patients were required to have weekly CBC and differential counts as well as complete chemistries and renal function tests every 21 days. Scans were repeated every 12 weeks for evaluation of tumor response. Non-hematologic ECOG grade 2 toxicity required 25% dose reduction and grade 3 toxicity, 50% reduction. In the event of grade 4 non-hematologic toxicity, patients were required to be removed from study.

Statistical methods included a two-stage design with an early stopping point after the first 17 patients were accrued, assuming at least 15 were evaluable for response without a single objective response. The primary endpoint for this study was tumor response determined by an exact binomial distribution with the 90% confidence interval calculated from the estimate of the response rate. Survival was also correlated with prognostic variables at the time of study entry by log-rank test[14] and Cox's proportional hazard regression.[15]

Results and discussion

Seventeen patients (Table 1) were accrued to this study between 31 August and 13 November 1987, at

Table 1. Patient characteristics

Entered	17
male	11
female	6
Performance status	
0	7
1	5
2	5
Histology	
lentigo maligna	10
superficial spreading	3
unknown	4
Prior immunotherapy	
yes	6
no	11
Prior radiotherapy	
yes	3
no	14
Extent of disease	
soft tissue only	4
lung	10
liver	5
adrenal gland	3
GI tract	1
brain	1

which time accrual to the study was suspended according to the early stopping rules. Seventeen patients were accrued included six females and 11 males all of whom had metastatic melanoma. Median age of this group was 52 years (range 27–75). Eleven of the 17 patients had visceral metastases to the lung, liver or intestines. Three of the patients had received prior radiation therapy and two had received prior immunotherapy with lymphokine activated killer cells and interleukin-2.

All patients were eligible for therapy and were treated with at least one dose of melphalan. The median number of cycles per patient was 2; however, one patient with stable disease received 13 cycles of melphalan until he eventually progressed. The non-hematologic toxicity of this regimen was limited. Three patients experienced severe non-hematologic toxicity, one with severe vomiting and two with severe pain.

One patient was inevaluable for hematologic toxicity since interim blood counts were not collected. Fifty-six percent (nine of 16) experienced severe or worse hematologic toxicity, including seven patients with grade 3 and one with grade 4 leukopenia. One patient developed grade 3 and one grade 4 thrombocytopenia. Of the 12 patients receiving more than one cycle, two were dose reduced for myelosuppression once and two were reduced for myelosuppression twice. Fifty-nine percent (10 of 17) reported severe or worse toxicity of any kind. The incidence of various complications related to treatment is presented in Table 2. The worst degree of any type of toxicity per subject is given in Table 3.

Table 2. Incidence of severe and life-threatening toxicity

Toxicity	Severe	Life threatening
Vomiting	1	
Leukopenia	7	1
Thrombocytopenia	1	1
Anemia	1	
Pain	2	

Table 3. Worst toxicity per patient

Grade	Percent
None	6
Mild	6
Moderate	29
Severe	47
Life threatening	12

There were no responses reported on this protocol among the 16 patients evaluable for response. One patient was determined to be inevaluable for response, having died of unknown causes at 25 days after entry to the study. One patient with lung nodules was stable for 13 cycles before progression. The exact binomial 90% confidence interval is 0–17% given the 0% estimate of the true response rate. Median survival for the patients entered in this trial was 3.5 months. Survival was correlated with patient characteristics by a two-sided log-rank test for the unadjusted association with survival. Metastatic disease sites of liver, skin and adrenal gland were individually associated with poorer survival. These factors, as well as performance status, age, gender and prior radiotherapy were considered in a step-down Cox model procedure. Only the two factors of distant liver and adrenal gland metastases were found to emerge as simultaneously prognostic for shorter survival. This analysis should be considered exploratory since it is based on 17 patients only.

The ECOG conducted this study (EST 1687) with i.v. melphalan based on the theoretical considerations of the activity of melphalan in melanoma. The dose of 30 mg/m^2 used here is not as high as been used in some i.v. chemotherapy programs, though in this previously untreated group of patients, it was associated with a high degree of grades 3 and 4 toxicity. The patients who remained on study for multiple cycles universally required dose reductions as the cumulative bone marrow suppressive effects of this agent became evident in the blood counts. No responses were seen in this study, although one patient remained stable for 13 cycles. One patient with early death on study was not evaluable for response. Response rate for this program was 0%, with the 90% confidence interval extending to 17% maximum.

We conclude that conventional-dose melphalan is inactive in the treatment of metastatic malignant melanoma. High-dose programs and isolated limb perfusion may have activity due to their ability to deliver this drug in higher concentrations without dose-limiting myelosuppression. Future directions for the use of melphalan may include the use of this drug in those settings, as well as biochemical modulation with agents such as BSO and other modulators of gluthathione synthesis.

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