Acute Rhabdomyolysis after Concurrent Administration of Interleukin-2, Interferon-Alfa, and Chemotherapy for Metastatic Melanoma

Paolo Anderlini, M.D., Antonio C. Buzaid, M.D., and Sewa S. Legha, M.D.

Background. **Acute rhabdomyolysis has been described to occur only rarely after systemic administration of cancer chemotherapy drugs, such as cytarabine and 5-azafluorene. A single case of rhabdomyolysis after treatment with alfa-interferon recently was reported, but to the authors' knowledge, there have been no published cases of clinically relevant rhabdomyolysis after systemic therapy with the other agents.**

Methods. **The case of a 28-year-old woman with metastatic melanoma and no known history of neuromuscular disorders who developed severe myalgia followed by acute, extensive rhabdomyolysis with multiorgan failure after concurrent administration of systemic biologic therapy and chemotherapy consisting of alfa-interferon, interleukin-2, cisplatin, vinblastine, and dacarbazine is described.**

Results. **The patient sustained considerable morbidity requiring hemodialysis and respiratory support but eventually recovered. Review of the literature revealed no reported cases of acute rhabdomyolysis after the systemic administration of these agents with the exception of alfa-interferon.**

Conclusion. **Acute rhabdomyolysis should be considered when evaluating patients receiving similar biochemotherapy regimens, particularly for those regimens that are alfa-interferon–based and for patients who develop myalgia along with evidence of multiorgan failure.** ***Cancer*** **1995;76:678–9.**

Key words: malignant melanoma, rhabdomyolysis, alfa-interferon, interleukin-2, cisplatin, vinblastine, dacarbazine.

From the Department of Melanoma/Sarcoma Medical Oncology, The University of Texas M.D. Anderson Cancer Center, Houston, Texas.

Address for reprints: Antonio C. Buzaid, M.D., Department of Melanoma/Sarcoma Medical Oncology—Box 77, The University of Texas M. D. Anderson Cancer Center, 1515 Holcombe Blvd., Houston, TX 77030.

Received January 23, 1995; revision received March 31, 1995; accepted March 31, 1995.

The antitumor effects of chemotherapy and biotherapy when used alone in treating metastatic melanoma remain disappointing. The combination of these two treatment modalities, referred to as biochemotherapy, currently is being investigated as a promising, albeit potentially toxic, approach to improve the outcome of patients with melanoma with advance disease.[1] We report the case of a patient who developed acute rhabdomyolysis and multiorgan failure after systemic biochemotherapy with concurrent administration of cisplatin, vinblastine, dacarbazine, alfa-interferon, and interleukin-2. To our knowledge, with the exception of alfa-interferon, this complication has not been described previously for the systemic use of these agents.[2]

Case Report

A 28-year-old Brazilian woman without other known medical problems was referred to our institution for recurrence of a malignant melanoma of the right thigh. The extensive locoregional recurrence involved the right internal iliac lymph nodes. The patient previously underwent resection of a melanoma metastatic to the ovary. She began receiving a biochemotherapy regimen consisting of cisplatin (20 mg/m^2/day intravenously on Days 1–4), vinblastine (1.6 mg/m^2/day intravenously on Days 1–4), dacarbazine (800 mg/m^2/day intravenously on Day 1), alfa-interferon (5 million U/m^2/day subcutaneously on Days 1–5), and interleukin-2 (9 million U/m^2/day by continuous intravenous infusion on Days 1–4). The combination regimen was followed by granulocyte-colony stimulating factor 300 μg/day subcutaneously from Day 5 to 11. Her antiemetic medications were ondansetron (32 mg intravenously four times/day on Days 1–5), lorazepam (0.5 mg intravenously every 8 hours on Days 1–5), and prochlorperazine 10 mg intravenously plus diphenhydramine 25 mg intravenously every 6 hours around the clock on Days 1–5.

The patient, as expected, had episodes of fever on Days 1–5 that reached a maximum of 39.4°C on Day 3 and lasted an average of 3 hours (range, 2–4 hours) but became afebrile thereafter. Approximately 36 hours after completion of the

first course of therapy, she developed severe, generalized myalgias. She subsequently went into hemodynamic shock and was transferred to the intensive care unit. She required pressors, ventilatory support for respiratory fatigue, and hemodialysis for oliguric acute renal failure. Laboratory evaluation showed markedly increased serum creatinine kinase levels (peak >32,000 U/L, 98% MM isoenzyme fraction), myoglobinuria, metabolic acidosis (lowest bicarbonate level 11 mmol/L), lactic acid (peak 13.7 mmol/L), hyperkalemia (peak 6.8 mmol/L), hyperphosphatemia (peak 2.8 mmol/L), and hypocalcemia (lowest level 1.1 mmol/L). She remained afebrile, multiple blood cultures were negative, and X-rays showed no evidence of pulmonary infiltrates. Her neurologic examination disclosed only generalized muscle weakness. Thyroid function tests were within the normal range. Her serum creatinine level peaked at 353 μg/L before gradual recovery of baseline kidney function. Muscle biopsy showed scattered necrotic myofibers and a scant macrophage infiltrate, with unremarkable blood vessels, nerve bundles, and connective tissue. Electron microscopy examination failed to reveal additional abnormalities. The patient required ventilatory support for 9 days and hemodialysis for 3 weeks. She gradually improved and eventually was discharged to continue physical therapy and rehabilitation. Because the patient chose to return to Brazil, no further diagnostic workup to detect any underlying myopathies were able to be performed. She achieved a partial response, and, to date, remains in remission after more than 6 months.

Discussion

The patient described in this report developed acute, massive rhabdomyolysis shortly after completing her first biochemotherapy course. Without other known causative factors, it appears likely that the episode was triggered by the biochemotherapy. Acute rhabdomyolysis is a well recognized clinical syndrome[3] that has been described only rarely after systemic administration of cancer chemotherapy drugs, such as cytarabine and 5-azacytidine.[4–6] In addition, acute muscle toxicity and myoglobinuria after hyperthermic isolated limb perfusion with high dose cisplatin[7] or a combination of tumor necrosis factor and melphalan[8] have been described. A case of rhabdomyolysis after treatment with alfa-interferon recently was reported,[2] but we are not aware of published cases of clinically relevant rhabdomyolysis after systemic therapy with the other agents, used alone or in combination, in our patient's regimen (including granulocyte-colony stimulating factor). Although the patient received prochlorperazine, she lacked the diagnostic criteria for the neuroleptic malignant syndrome.[9]

The pathophysiology of this idiosyncratic reaction in our patient and the contribution of the individual agents used remains unclear. It is tempting to speculate that cisplatin and/or high concentrations of endogenously released or exogenously administered cytokines may cause acute, extensive muscle injury in patients with undiagnosed or subclinical myopathies. Regardless, the possibility of acute rhabdomyolysis should be considered when evaluating patients receiving similar biochemotherapy regimens who develop severe myalgias.

References

1. Buzaid A, Legha S. Combination of chemotherapy with interleukin-2 and interferon-alfa for the treatment of advanced melanoma. *Semin Oncol* 1994;21:23–8.
2. Greenfield S, Harvey R, Thompson R. Rhabdomyolysis after treatment with interferon alpha. *Br Med J* 1994;309:512.
3. Gabow P, Kaehny W, Kekkeher S. The spectrum of rhabdomyolysis. *Medicine* 1982;61:141–52.
4. Margolis D, Ross E, Miller K. Rhabdomyolysis associated with high-dose cytarabine. *Cancer Treat Rep* 1987;71:1325–6.
5. Papakonstantinou C, Papanastasiou K, Kotsopoulou K, Mouratidou M, Sotiropoulos D, Kyrtsoni M, et al. Chemotherapy-related acute rhabdomyolysis. *J Natl Cancer Inst* 1992;84:536–7.
6. Koeffler H, Haskell C. Rhabdomyolysis as a complication of 5-azacytidine. *Cancer Treat Rep* 1978;62:573–4.
7. Fletcher W, Woltering E, Moseley S, Bos G, Lebredo L, Brown D, et al. Hyperthermic isolation limb perfusion (HILP) in the management of extremity melanoma and sarcoma with particular reference to the dosage, pharmacokinetics, and toxicity of cisplatin. *Cancer Treat Res* 1993;62:241–4.
8. Hohenberger P, Haier J, Zaiac M, Schlag P. Rhabdomyolysis after isolated TNF/melphalan limb perfusion detected by myoglobin and creatinkinase monitoring. *Proc Am Soc Clin Oncol* 1994;13:1652.
9. Caroff S, Mann S, Lazaruz A. Neuroleptic malignant syndrome: diagnostic issue. *Psychiatr Ann* 1991;21:130–47.