Cancer Chemother Pharmacol (1985) 15: 174–175

Cancer Chemotherapy and Pharmacology

Nephrotoxicity of lomustine

A case report and literature review*

Mark E. Ellis[1, 2], Raymond B. Weiss[1, 2], and Mario Kuperminc[3]

[1] Section of Medical Oncology, Walter Reed Army Medical Center, Washington, DC 20307-5001, USA
[2] Uniformed Services University of the Health Sciences, Bethesda MD 20814, USA
[3] Hematology-Oncology Associates of Virginia, Richmond, VA 23226, USA

Summary. *A patient is presented who developed nephrotoxicity after therapy with lomustine (CCNU) for astrocytoma of the brain. Only three other cases of lomustine nephrotoxicity have been reported, and all cases have been associated with cumulative drug doses of greater than 1,500 mg/m². The clinical and pathologic features of lomustine nephrotoxicity are reviewed. It is recommended that cumulative doses of more than 1,200–1,400 mg/m² lomustine be avoided because of the risk of nephrotoxicity.*

Introduction

Nephrotoxicity is a well-recognized adverse side effect of several cancer chemotherapeutic agents, most notably cisplatin and streptozocin. The latter drug is a member of the nitrosourea group. Other nitrosoureas, such as lomustine (CCNU) and semustine (methyl-CCNU), have also demonstrated renal toxicity in both preclinical toxicologic and clinical studies [3, 5]. Semustine appears to have the greater risk of nephrotoxicity in humans, especially when cumulative doses of greater than 1,200–1,500 m/m² are used over long periods of time [6]. It is of interest that in some cases such toxicity may be delayed until months after completion of chemotherapy with semustine. Although nephrotoxicity from semustine and streptozocin are significant problems, only three cases of nephrotoxicity induced by lomustine have been reported to date [1, 2, 4]. We report a fourth case of lomustine-induced nephrotoxicity and review the clinical and pathologic features of this case, which are similar to those observed in the three previously reported cases.

Case report

A 29-year-old white man was admitted to the hospital in Richmond, Virginia in December 1976 with a 2-month history of intermittent bifrontal headaches. The physical examination was unremarkable except for bilateral papilledema, and a CT scan of the brain revealed a large right frontal lobe mass. The patient underwent partial removal of the mass, which proved to be a grade III astrocytoma. He then started treatment with lomustine 200 mg (100 mg/m²) PO every 5 weeks. Prior to treatment with lomustine he had normal blood counts, normal serum chemistry (including normal BUN and creatinine), and a normal urinalysis. Over the next 26 months the patient received 3,530 mg lomustine (approximately 1,700 mg/m²), with occasional dose reduction secondary to hematologic toxicity (leukopenia). His clinical course remained stable without evidence of tumor progression on serial CT scans. In April 1979 he was admitted to a local hospital for evaluation of right-sided pneumonitis, the cause of which could not be elucidated after an exhaustive investigation. The infiltrate cleared after 2 weeks of erythromycin therapy, but because of the suspicion that this may have been a manifestation of pulmonary toxicity from lomustine his chemotherapy with lomustine was discontinued. The BUN at that time was 14 mg%.

The patient remained stable clinically. His BUN was 18 mg% in October 1979, 24 mg% in February 1980, and 30 mg% in October 1980 (normal: 10–26 mg%). Later, in October 1980 the patient was admitted with apparent bacterial meningitis and was treated with penicillin and chloramphenicol with resolution of his symptoms. No nephrotoxic agents were used during this hospitalization, and the patient's BUN remained in the 27–30 mg% range. His creatinine was noted to be 2.4 mg%. Over the next 3.5 years the renal function remained stable with BUN 30–35 mg%, creatinine 2.5–2.7 mg%, and normal urinalysis.

In March 1984 the patient expired from complications of progressive astrocytoma in the brain. He had used no other medications chronically during the period of observation. At autopsy the kidneys revealed extensive glomerular hyalinization believed to be compatible with effects of chemotherapy, especially since the degree of atherosclerotic vascular disease in the kidneys was not significant enough to produce such a degree of glomerular hyalinization. (Fig. 1). No other readily identifiable cause for these renal changes could be detected. The renal tubules were normal, except for minimal scattered dystrophic calcification.

Discussion

Lomustine has been shown to be an effective chemotherapeutic agent, especially in the treatment of brain tumors and in combination with other agents for the treatment of small cell carcinoma of the lung. In 1979 Silver and Mor-

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Offprint requests to: R. B. Weiss

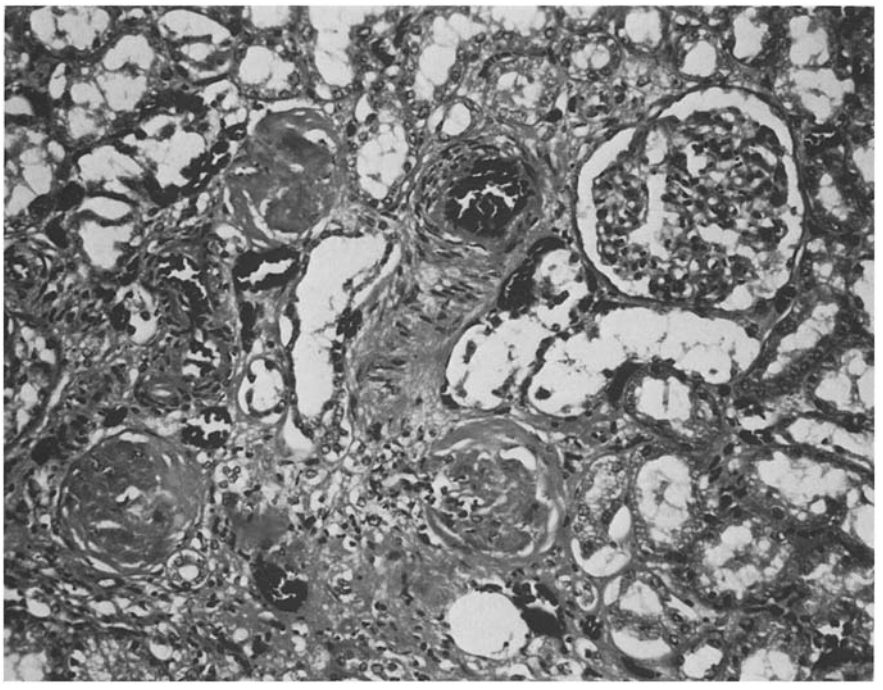

Fig. 1. Histology of the kidney obtained at autopsy, demonstrating three hyalinized glomeruli and one nearly normal glomerulus (H & E, original magnification × 160)

ton [4] reported a patient with small cell carcinoma of the lung, who had a 3-year remission from her tumor but who died of complications of renal failure. This renal failure was believed to be secondary to lomustine toxicity after the patient had received a cumulative dose of 2.3 g lomustine. In 1980 Berglund [1] reported a case of progressive renal insufficiency discovered after the patient had received a cumulative lomustine dose of 1,790 mg/m^2. The patient did not have proteinuria or other pathologic urinary sediment, and at autopsy similar pathologic findings to our case were noted in the kidneys, i.e., extensive glomerular sclerosis. Also in 1980, another case of terminal chronic renal failure related to a lomustine dose of 1,940 mg/m^2 was described [2], and a maximum safe cumulative dose for lomustine of 1,200 mg/m^2 was suggested to prevent this complication.

With the addition of our case to these previous reports, it appears that there is a danger of nephrotoxicity from lomustine, especially when it is given in large cumulative doses over prolonged periods of time. As has been suggested previously [4], the duration of tumor response to therapy with lomustine and its nephrotoxicity may be related, in that a long duration response allows for the total dose accumulation associated with such toxicity. This experience of nephrotoxicity from lomustine is similar to that recorded with semustine, where a cumulative dose of 1,200–1,400 mg/m^2 implies a high risk of nephrotoxicity [6]. Moreover, as seen in our case and as has been reported with semustine [6], the manifestations of renal toxicity may be delayed until after the completion of therapy.

Weiss et al. [6] were able to collect 35 cases of nephrotoxicity from semustine, even though this drug is still investigational and is not freely available. However, there have been only four published cases of nephrotoxicity related to lomustine, a drug which is on the market and is widely used in the treatment of a common cancer, small cell lung cancer. The reason for this difference is not apparent. The drugs are very similar chemically. Whether there is any difference in metabolism and metabolite effect on the kidney is not known. There is little reason to think that the difference is based on cumulative dose, because the individual doses used are similar and approximately the same small fraction of patients receiving each drug would be expected to reach a cumulative dose of 1,400 mg/m^2 or greater.

Myelosuppression continues to be the main toxicity of lomustine, but nephrotoxicity may also occur, and it is advisable to monitor renal function periodically in patients so treated. In addition, it seems prudent to limit the cumulative dose of lomustine to 1,200–1,400 mg/m^2 to avoid the potentially life-threatening complication of renal failure.

Acknowledgement. The authors thank Miss Cathy Morris for typing this paper.

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Received September 17, 1984/Accepted November 20, 1984