The use of high-dose acyclovir in patients with hematological malignancies who develop herpes virus infections: Is it really safe?

Hematolojik hastalığı olan herpes virusu gelişen hastalarda yüksek doz asiklovir kullanımı. Gerçekten güvenli mi?

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Infections with herpes viruses are a common phenomenon in patients being treated for hematological malignancies who undergo stem cell transplantation (SCT). The safe use of high-dose acyclovir in these patients has been established in numerous clinical trials [1]. Most reported adverse effects are tolerable and generally reversible [1]. Life-threatening effects such as severe neurotoxicity or nephrotoxicity have rarely been reported in the documented literature [2,3]. Therefore, we hereby share our experience regarding a patient with plasma cell leukemia who developed severe neurotoxicity and irreversible nephrotoxicity due to high-dose acyclovir.

A 42-year-old female with resistant plasma cell leukemia was admitted to our hematology unit. Type II diabetes mellitus (DM) had been diagnosed 10 years before. EDAP chemotherapy regimen was initiated in the patient and she was discharged on day 9. On day 16, she was readmitted with neutropenic fever and herpes labialis infection. The patient's white blood cell count and platelet count were $2.2x10^9/mm^3$ (20% PMNL) and $22x10^9/mm^3$, respectively. Renal and hepatic function tests and serum calcium level were normal. Urine examination revealed 3+ protein, and 3 to 5 white blood cells. At the point of hospitalization, urine output was approximately 2300 ml/day. Cefepime (2 g intravenously every 8 hours) was initiated according to febrile neutropenia protocol. Additionally, high-dose acyclovir (1500 mg/m^2) was added to the therapy because the underlying disease was not under control. On day 3, serum creatinine levels increased to 5.1 mg/dl and she became confused and developed periods of unconsciousness. Her blood pressure was 120/70 mmHg, with a heart rate of 98 beats per minute. Urine output was 800 ml/day and urine sediment revealed 1 to 2 white blood cells, and 6 to 7 white blood cells, consecutively. Urine quantitative analysis of the patient revealed osmolarity of 270 mOsm, urinary sodium of 70 mEq/L, fractional excretion of sodium of >1% and proteinuria of 2.1 g/dl.

On the same day, a cranial tomographic scan ruled out cerebral tumor and hemorrhage. The cerebrospinal fluid had a mildly elevated protein level (0.50 g/L), but no malignant cells were found. In addition, bacterial and viral cultures were negative, and an electroencephalogram showed diffuse slowing and no seizure activity. Serum electrolytes, glucose, and acid-base status were normal. On day 5, we discontinued the use of acyclovir upon consideration of the adverse effects of acyclovir-induced consciousness disturbances and acute renal failure.

Two days later, a clinical improvement was seen in her level of consciousness. She was able to respond to pain and open her eyes spontaneously. On day 12, she became increasingly alert, could answer questions appropriately, and began to walk. Further, four days after the discontinuation of acyclovir, urine output increased to 3400 ml/day, and serum creatinine level decreased to 3.2 mg/dl. Creatinine levels did not return to nor-

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mal but remained constant for subsequent days, although high urine output was observed. She was discharged and recommended as a recipient for allogeneic SCT.

Acyclovir neurotoxicity is a self-limiting, dose-dependent, rare phenomenon that is more likely to occur in elderly patients. It is distinguished from viral encephalitis by its sudden onset, absence of fever or headache, lack of focal neurological findings and normal cerebrospinal fluid [4]. It should be emphasized that patients with acyclovir neurotoxicity may not have renal insufficiency before receiving acyclovir, as was the case with our patient. The most common manifestations of acyclovir neurotoxicity are confusion, delirium, hallucinations, lethargy, and mild tremors. The neurological status of our patient with resolution of symptoms within approximately one week of acyclovir withdrawal is in agreement with other reports on acyclovir toxicity [5].

Acyclovir-induced nephrotoxicity is well known and is also uncommon, like its neurotoxicity. Furthermore, it is more common in patients treated with high- dose cytotoxic chemotherapy than in other patient populations treated with acyclovir. Acute renal failure mediated by this compound is characterized by abrupt elevations in serum creatinine and a gradual return to baseline renal function upon discontinuation of the drug. Since our patient had DM type 2, and proteinuria was determined in her routine examination before chemotherapy, DM with proteinuria might have predisposed her to irreversible renal function abnormalities in the presence of acyclovir. When such patients with subclinical renal disorders have elevated serum creatinine levels in conjunction with acyclovir therapy, the acyclovir should be considered as a potential cause. Additionally, acyclovir, cefepime, and also cisplatin, which were used in the chemotherapy regimen, are eliminated by both glomerular filtration and tubular secretion. It is possible that the interaction of these drugs partly contributed to the tubular damage [6].

Due to our report lacking a renal biopsy, we were unable to document any pathological changes. We could not perform renal biopsy because of the low performance status of the patient. Additionally, our report did not include a record of serum acyclovir levels. However, measurement of acyclovir levels is not practical or useful for the diagnosis of acyclovir neurotoxicity because the assay is not widely available and the delay imposed by handling specimens and receiving results reduces the test's utility [7].

In conclusion, severe acute renal failure and neurotoxicity may be associated with intravenous acyclovir. This case suggests that patients being treated by standard or high-dose chemotherapy with subclinical renal abnormalities (e.g. history of DM, proteinuria or nephrotoxic drugs) may be at an increased risk and should be monitored closely for signs and symptoms of acute renal failure and neurotoxicity while receiving acyclovir. Physicians involved with high-dose chemotherapy and SCT must be alert to other potentially toxic medications that are being used for the primary disease or other disease-related problems.

References

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