therapeutic high-dose (≥50 Gy) irradiation for head and neck cancer and lymphomas when the lower dose (approximately 40 Gy) radiation volume encompasses the submandibular and sublingual salivary complexes. Far more prevalent is xerostomia resulting from autoimmune diseases, of which the most commonly identified is Sjögren’s syndrome. Sjögren’s syndrome is also characterized by other xeroses with xerophthalmia identified as the other defining presentation of this syndrome.

Earlier work emanating from the National Institute of Dental Research and other sources gave evidence that the plant alkaloid pilocarpine hydrochloride might have value in treating xerostomia induced from irradiation or autoimmune sicca (2–4). In 1990–1991, two parallel phase III trials using an oral formulation of pilocarpine hydrochloride to treat post-radiation-therapy xerostomia demonstrated that this agent was safe and efficacious (5,6). On the basis of data from these trials, oral pilocarpine was licensed by the U.S. Food and Drug Administration (FDA) for prescriptive sale for this indication.

Later, we used oral pilocarpine preemptively in head and neck cancer patients scheduled to receive radiation therapy. Entry criteria mandated a radiation dose of 50 Gy or more to the primary tumor, which had to be located in the oral cavity, oropharynx, or nasopharynx, thus ensuring inclusion of maximum salivary parenchyma in the radiation volume (7). This study far exceeded the protocol hypothesis, which was that concurrent use of pilocarpine would shelter 30% or more of baseline salivary flow. This hypothesis will be further tested in a National Cancer Institute-sponsored phase III trial conducted by the Radiation Therapy Oncology Group to begin in late 1997. If successful, the prophylactic use of pilocarpine hydrochloride in head and neck cancer radiation could become the standard of care. Recently completed phase III trials in which oral pilocarpine was used to treat autoimmune sicca in Sjögren’s syndrome showed a statistically significant improvement in all protocol end points (Vivino FB, Al-Hashimi I, Khan Z, LeVeque F, Salisbury P, Tran Johnson T, et al.: unpublished data). The resulting data from these investigations have been submitted to the FDA as an application for this additional therapeutic indication for use of oral pilocarpine. An interesting finding in one of the phase III Sjögren’s syndrome studies was the statistically significant clinical improvement of vaginal xerosis in female subjects. We are currently conducting a trial to see if oral pilocarpine can induce vaginal moisture in younger women with stage IIa and IIb breast cancer who have suffered ovarian dysfunction from adjuvant or high-dose chemotherapy with stem cell rescue.

The search for viable therapies of preventions for dry mouth is not moribund, nor is current available therapy relegated to use of saliva substitutes and other exogenous topical moisturizers. The ability to genetically engineer ex post facto repair of salivary gland damage or to prevent it by protective means is a salutary goal that will provide an even greater clinical benefit.

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Editor’s note: The author owns stock in MGI Pharma, Inc., manufacturer of the pilocarpine hydrochloride used in this study.

References


Note

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Gemcitabine-Induced Hemolytic Uremic Syndrome: A Case Report

Hemolytic uremic syndrome (HUS) is a rare side effect of chemotherapeutic agents reported in patients treated with cisplatin and bleomycin (1), mitomycin C (2), and high-dose chemotherapy in general (3). Gemcitabine is an effective drug for systemic therapy of non-small-cell lung cancer (NSCLC) (4) and has few, well-defined side effects (5). One report (6) has been published about a mild HUS that appeared related to gemcitabine therapy. This report is to extend this observation in one patient who developed severe HUS in connection with the administration of gemcitabine therapy.

A 45-year-old Caucasian male was diagnosed with NSCLC (World Health Organization stage I, T2N0M0) of the right middle lobe in September 1994, and pneumonectomy was performed. Histology revealed free resection margins. In November 1996, the patient developed thoracic metastases. Subsequently, intravenous gemcitabine therapy (1250 mg/m² on days 1, 8, and 15, administered over a 30-minute period, repeated every 28 days) was initiated. Antiemetic prophylaxis consisted of 3 mg granisetron given intravenously.

After cycle 6 (cumulative dose, 21250 mg/m²), the patient presented with fever (37.8 °C), mild jaundice, and a blood pressure of 200/110 mm Hg. Laboratory analysis showed the following pathologic values (normal ranges in parentheses): creatinine, 4.3 mg/100 mL (0.5–1.3); blood urea nitrogen, 39 mg/100 mL (6–25); hemoglobin, 6.5 g/dL (12–17); platelets, 60 × 10⁹/L (150–350); haptoglobin, <12 mg/dL (50–320); reticulocytes, 3.6% (3%–15%); schistocytes (fragmented red blood cells), 1.2% (0%); unconjugated bilirubin, 2.26 mg/
100 mL (0–1); and lactate dehydrogenase, 700 U/L (120–240). Urinary analysis showed mild proteinuria, microscopic hematuria, and cylindruria. Kidney biopsy demonstrated occlusion of small renal arteries as a result of mucoid widening of the intima and occasional presence of fibrin thrombi (Fig. 1, A). There was also prominent thickening of the glomerular capillary walls with double-contour appearances (Fig. 1, B). Moderate, diffuse interstitial fibrosis and chronic tubular damage were observed. Despite immediate treatment with prednisolone and plasmapheresis, the patient developed dialysis-dependent chronic renal failure. Hemolysis ceased after 3 weeks.

We believe that the patient’s clinical presentation and laboratory and histologic findings are pathognomonic for HUS, which occurred in conjunction with gemcitabine administration. Other putative mechanisms implicated in the etiology of HUS such as infections or disseminated intravascular coagulation can be ruled out by normal C-reactive protein and leukocyte levels, x-ray of the lung without evidence of an inflammatory infiltrate, and normal results of agglutination tests. In contrast to thrombotic thrombocytopenic purpura, this disorder remained localized to the kidney.

Since the patient’s only medications were granisetron and gemcitabine, and no granisetron-induced HUS has been reported so far, the administration of gemcitabine was most likely the reason for the patient’s clinical presentation. However, no clear conclusion about dose dependency of gemcitabine can be derived because the patient described here developed severe HUS after the cumulative gemcitabine dose was 21,250 mg/m², in contrast to the previously reported mild HUS (6), where 800 mg/m² gemcitabine had been administered. It is noteworthy, however, that this drug, which is known to be well tolerated and exerts few and mild side effects (5, 6), was able to induce the severe condition reported above.

Fig 1. A) Small renal artery with occluded lumen. Distinct mucoid widening of the intima with remnants of fibrinous material can be observed (arrow) (periodic acid–Schiff stain, original magnification ×200). B) Prominent thickening of the glomerular capillary wall with double-contour appearances (arrowhead) (methenamine-silver stain, original magnification ×400).

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References


Notes

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Erratum: “Cofactors With Human Papillomavirus in a Population-Based Study of Vulvar Cancer,” by Madeleine et al. [J Natl Cancer Inst 1997;89:1516–23 (Issue 20)]. On page 1519, the last category in column 1 of Table 3 should read HSV2 and not HPV2. In addition, in the Notes section on page 1523, M. E. Hagensee, and not M. E. Madeleine, was supported by a Physician’s Training grant from Howard Hughes Medical Center. The Journal regrets the errors.