Valganciclovir in Patients with Glioblastoma

TO THE EDITOR: Söderberg-Nauclér et al. (Sept. 5 issue) report that cytomegalovirus (CMV) antigens are detected in more than 99% of human glioblastomas. In their trial, in which the benefit of valganciclovir was evaluated in patients with glioblastoma, 29% of the 42 participating patients were seronegative for CMV IgG, a result similar to that obtained in larger studies. A large proportion of the patients with intratumoral expression of CMV antigens are therefore unlikely to have had CMV infection.

In a recent large-scale analysis of transcriptome-sequencing data of viral nucleic acids, significant levels of CMV RNA were not detected in human gliomas (glioblastoma multiforme). Out of 22.8 billion sequencing reads from 167 tumors, only 1 sequence corresponded with CMV RNA. These results imply that CMV does not replicate in gliomas and thus that treatment with virus-replication inhibitors, such as valganciclovir, may be futile. Questions regarding the intratumoral expression of CMV antigens in seronegative patients and the apparent lack of intratumoral replication of CMV should be resolved before larger trials of valganciclovir in glioma are initiated.

Kristoffer Hellstrand, M.D., Ph.D.
Anna Martner, Ph.D.
Tomas Bergström, M.D., Ph.D.
University of Gothenburg
Gothenburg, Sweden
kristoffer.hellstrand@gu.se

No potential conflict of interest relevant to this letter was reported.


THE AUTHORS AND A COLLEAGUE REPLY: Current evidence suggests that CMV does not replicate in glioblastoma. CMV is found in 90 to 100% of glioblastomas with the use of polymerase-chain-reaction assays, immunohistochemical analysis, Western blot analysis, and CMV deep-genome sequencing, although large-scale DNA and RNA transcript sequencing have failed to detect CMV nucleic acids. Even though few tumor cells are positive for CMV DNA, many cells in glioblastomas are positive for CMV proteins. Thus, the biology of CMV in glioblastoma is not fully understood and is more complex than currently appreciated.

Clearly, many patients with glioblastoma have CMV infection without levels of IgG or IgM antibodies that can be detected by means of conventional enzyme-linked immunosorbent assays. Clinical virologists are therefore encouraged to improve the clinical diagnostics for CMV in patients with glioblastoma.

Valganciclovir inhibits tumor growth in vitro and in animal xenograft studies of tumors that are CMV-positive, but not in tumors that are CMV-negative, and it has greatly improved survival rates among patients with glioblastoma, possibly by inhibiting the late expression of CMV proteins and CMV-induced regulatory mechanisms. Further prospective, randomized clinical trials are needed to determine whether valganciclovir truly extends survival in patients with glioblastoma by as much as four times that in patients not receiving valganciclovir, and these trials should be conducted concomitantly with studies intended...
Visualization of Ectopic Parathyroid Adenomas

TO THE EDITOR: Ectopic parathyroid adenomas constitute a diagnostic challenge. The precise preoperative localization of these tumors in a patient with primary hyperparathyroidism may enable targeted surgical strategies that limit explorative surgery. The preoperative imaging techniques currently in use include ultrasonography, sestamibi scintigraphy, and four-dimensional computed tomography (CT).

11C-methionine positron-emission tomography–CT (PET-CT), a highly sensitive technique for localizing parathyroid adenomas, provides additional information that conventional imaging may not show. Simultaneous PET–magnetic resonance imaging (MRI) is a new hybrid method of imaging that permits exact fusion of molecular and high-resolution anatomical imaging that provides excellent soft-tissue contrast. This technique appears to have great potential in soft-tissue analysis of complex anatomical regions in which contrast-enhanced MRI has been superior to CT.

We present the case of a 60-year-old woman who had undergone thyroidectomy for nontoxic multinodular goiter and simultaneous parathyroidectomy of two of four parathyroid glands for suspected primary hyperparathyroidism. The histomorphologic features revealed one hyperplastic and one normal parathyroid gland. The postoperative level of serum calcium and parathyroid hormone remained elevated. Ultrasonography and technetium-99m–labeled sestamibi scintigraphy did not show evidence of a parathyroid adenoma in the cervical or mediastinal compartments (Fig. 1A). In addition, the patient underwent 11C-methionine PET-CT and, without further administration of a radiopharmaceutical agent, a 3-tesla simultaneous PET-MRI study. Both forms of imaging showed a metabolically active mass behind the left sternoclavicular joint. Delineation and anatomical attribution of this mass, however, was better with PET-MRI (Fig. 1B) than with PET-CT (Fig. 1C). Surgical resection was performed, and histologic analysis confirmed parathyroid tissue. The serum para-

Figure 1 (following page). Visualization of an Ectopic Parathyroid Adenoma in the Patient with the Use of Scintigraphy, PET-MRI, and PET-CT.

Panel A shows a planar technetium-99m–labeled sestamibi scintigraphic scan on the left and an axial technetium-99m–labeled sestamibi single-photon-emission CT scan on the right. Both are negative. Images courtesy of Drs. Christiane Volkheimer, Susanne Schenk, and colleagues, Center for Radiology and Nuclear Medicine am Johannisplatz, Leipzig, Germany. Panel B shows a metabolically active mass (arrows) in the upper anterior mediastinum that is suspicious for ectopic parathyroid tissue. The ectopic parathyroid tissue is detected by means of coronal 11C-methionine PET-MRI (image on the left), axial MRI (image on the top right), and axial 11C-methionine PET-MRI (image on the lower right). Panel C shows detection of this tissue by means of axial CT (left) and axial 11C-methionine PET-CT (right). The arrows indicate the hypermetabolic mass.


DOI: 10.1056/NEJMct1312413