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White Matter Disease Induced by High-Dose Chemotherapy: Longitudinal Study with MR Imaging and Proton Spectroscopy

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PURPOSE: **The purpose of this study was to determine the time course for development of white matter changes induced by high-dose chemotherapy.**

METHODS: **Eight patients with advanced breast cancer were entered into a prospective, longitudinal trial that included examination by MR imaging and proton MR spectroscopy before chemotherapy and through 12 months after treatment with carmustine, cyclophosphamide, and cisplatin, combined with autologous hematopoietic progenitor cell support (AHPCS).**

RESULTS: **Six patients completed induction chemotherapy, at which time all MR imaging studies appeared normal. At 3 months after the conclusion of high-dose chemotherapy and beyond, three of the four patients remaining in the study showed an increasing volume of white matter changes, which appeared to stabilize during the period from 6 months to 1 year. Maximal volumes of abnormal white matter ranged from 73 to 166 cm^3. MR spectroscopy showed little or no change in metabolic ratios through the period of observation, although there was a suggestion of small transient treatment-related decreases in the ratio of *N*-acetyl aspartate (NAA) to creatine.**

CONCLUSION: **White matter changes are common sequelae of treatment with high-dose chemotherapy combined with AHPCS, occurring early in the period following high-dose chemotherapy, with a rapid and progressive accumulation to about 6 months, but not accompanied by persistent neurologic symptoms. The MR spectroscopic analyses suggest a minimal disturbance of the neuronal marker NAA, a finding that may in part explain the good neurologic outcome.**

High-dose chemotherapy (HDC) with carmustine, cyclophosphamide, and cisplatin, with autologous hematopoietic progenitor cell support (AHPCS) has been adopted as a major and apparently effective approach to the treatment of advanced (stage II–IV) breast carcinoma (1). This therapeutic approach, however, according to the findings of two previous retrospective studies, results in a remarkable degree of white matter abnormality, detected as regions of T2-hyperintense signal on routine magnetic resonance (MR) imaging studies (2, 3). The significance of this white matter abnormality is unknown, as white matter changes are not associated with major clinically apparent and/or persistent neurologic sequelae. Previous in vivo proton MR spectroscopic studies have failed to show a significant disturbance in the neuronal marker *N*-acetyl aspartate (NAA) in patients who were examined in relatively late stages after HDC (2). However, white matter changes may still warn that limiting (neurotoxic) doses of chemotherapy have been reached or exceeded.

The purpose of this prospective pilot study was to determine the time course for development of HDC-induced white matter changes.

Methods

Eight subjects were randomly recruited from the pool of patients with advanced breast cancer (stage II–IV) who were undergoing preliminary evaluation for treatment in our university's bone marrow transplant program (see Table). All subjects, after informed consent and enrollment into clinical protocols, agreed to a prospectively designed course of examination by MR imaging and MR spectroscopy with the following timetable: at entrance into the study, after induction chemotherapy but before HDC, and at intervals of 1, 3, 6, 9, and 12 months after HDC/AHPCS therapy.

Recruitment into the study occurred over a 1-year period, and the overall duration of the study was 2 years. Eight patients had MR imaging/MR spectroscopy upon entry, and six had imaging studies through induction chemotherapy. Four pa-

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Entrance characteristics and summary results

Patient	Age, y	Cancer Stage on Entry	Acute Toxicity	Neurotoxicity	MR Imaging/MR Spectroscopy Studies	First Abnormal MR Finding	Comments
1	68	II	Atrial flutter	Hemianopsia, aphasia 2 mo after HDC/AHPCS	E, I, 1.5 mo, 5 mo, 7 mo, 11 mo	5 mo	Subdural hematoma, resolved spontaneously
2	46	IV	None	Vertigo since HDC/AHPCS	E, I, 2 mo, 3.5 mo, 6 mo, 9 mo, 13 mo	2 mo	···
3	44	IV	None	Optic nerve, within 6 mo after HDC/AHPCS	E, I, 2.5 mo, 7 mo, 10 mo	2.5 mo	···
4	38	IV	Renal	Tinnitus, since HDC/AHPCS; headache, numbness of fingers, two episodes, 2 mo after HDC/AHPCS	E, I, 1 mo, 3 mo, 5.5 mo, 9 mo, 12 mo	···	···
5	47	III	None	None	E	···	Discontinued for personal reasons
6	44	IV	Renal, pulmonary edema	None	E	···	Discontinued because of change in chemotherapy protocol
7	51	IV	Peripheral neuropathy	None	E, I	···	Discontinued because of change in chemotherapy protocol
8	41	IV	None	None	E, I	···	Discontinued owing to death (motor vehicle accident)

Note.—E indicates entry; I, postinduction chemotherapy.

tients were followed up with MR imaging/MR spectroscopy through 10 months to 13 months after HDC. Protocol timing deviations were frequent (see Table), as patients' visits were adjusted to accommodate scheduling conflicts. Two patients left the study owing to a change in their chemotherapy protocol, one patient died during the study as a result of injuries from a motor vehicle accident, and one patient elected to withdraw for personal reasons.

Patients were treated with HDC consisting of cyclophosphamide at 1875 mg/m^2 per day for 3 days as a 1-hour intravenous infusion, cisplatin at 55 mg/m^2 per day as a continuous intravenous infusion for 72 hours, and carmustine at 600 mg/m^2 as a 2-hour intravenous infusion on the fourth day, followed by AHPCS. Before HDC, the induction chemotherapy consisted of multiple cycles of doxorubicin hydrochloride, fluorouracil, and methotrexate. Patients were in some cases treated with other chemotherapeutic agents before entrance into the bone marrow transplant program, but none of the patients had prior or subsequent cranial X-radiation.

All MR imaging and MR spectroscopic studies were acquired on a 1.5-T system with the use of a standard bird cage head coil. The imaging protocol included a sagittal localizing image and axial T2-weighted spin-echo sequences with parameters of 2100/30,90/1 (repetition time [TR]/echo time [TE]/excitations), a 256 × 192 matrix, and a 22-cm field of view. In one patient, who had normal findings on the entrance study, imaging was performed with a 3-mm interleaved (nongapped) technique; otherwise, all studies were acquired with 5-mm-thick sections with a 2-mm gap. Before performing computerized segmentation to determine abnormal brain area and volume, a neuroradiologist annotated the films with a marking pencil to guide the subsequent analyses by an experienced image processor. Lesions were defined as newly developed hyperintensities on both long-TR/short-TE and long-TR/long-TE images. Total brain white matter abnormality was determined by using an in-house modification of a user-interactive semiautomated bifeature space-segmentation procedure (4), although with training and statistical segmentation in clusters of only one to three sections to minimize z-axis intensity variation–induced errors (5).

Single-voxel proton spectroscopy was performed as described previously (2) on 2 × 2 × 2-cm voxels centered in the right parietooccipital white matter adjacent to the lateral ventricle. The choice of this location was based on earlier experience, from which it was known that the parietooccipital region (right or left) was most likely to become the area in which the maximum change in white matter would occur (2, 3). Spectra were acquired from the same voxel in each patient throughout the study, using images of the previous voxel location as a guide to position. These studies were processed and analyzed by one spectroscopist, without reference to previous studies or to the timing of the study. Two spectra with TEs of 30 and 136 were acquired by using the stimulated-echo acquisition mode pulse sequence with a TR of 1600 and a mixing time of 13.7 milliseconds with 256 averages each, preceded by three frequency-selective (chemical-shift-selective) water-suppression pulses. Data size was 2048 points with a spectral width of 2000 Hz. Processing was performed on a SunSparc 2 workstation (Sun Microsystems, Sunnyvale, Calif) using the SA/GE processing software (GE Medical Systems, Milwaukee, Wis) and included zero-filling to 4096 points, 0.5-Hz line broadening, Fourier transformation, and manual phasing. The spectra were fit using Marquardt fitting and lorentzian line shapes to obtain fitted areas for each peak as described previously (2). Statistical analyses included the paired sample *t* test for a change in the means on the patient data between the first and the subsequent examinations.

Results

MR Imaging

All eight subjects had normal findings on MR images at study entry, with either no white matter abnormalities or areas of T2-hyperintense signal thought to represent minor, nonspecific findings and/or changes typical for age. After completion of induction chemotherapy, but before HDC/AHPCS,

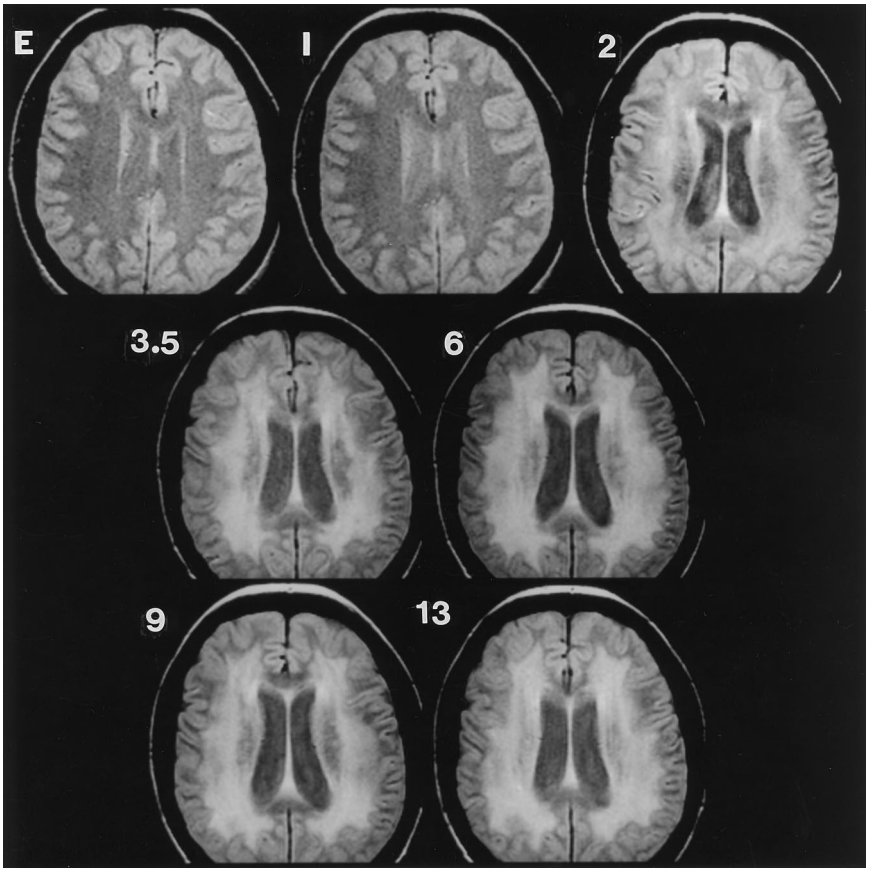

FIG 1. Serial evaluation of white matter changes. Long-TR/short-TE imaging in patient 2. Studies at entry (*E*), after induction chemotherapy (*I*), and at 2, 3.5, 6, 9, and 13 months after HDC/AHPCS. Note the progressive increase in abnormal white matter first detected on the 2-month study. The volume of expanding abnormal white matter appeared to stabilize at about 6 months.

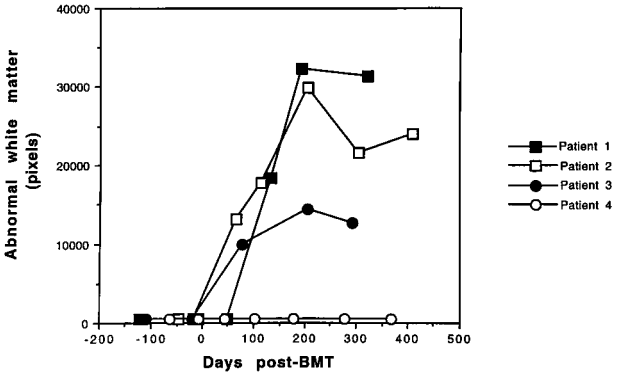

FIG 2. Serial evaluation of changes in abnormal white matter. Results are shown for the four patients studied after HDC/AHPCS. Abnormal white matter is expressed as the number of abnormal pixels. Maximal volume of abnormal white matter can be estimated on the basis of the assumption that 10 000 pixels = 50 cm^3 of abnormal white matter, if a lesion fills the section and intersection completely. *BMT* indicates day of bone marrow transplantation (AHPCS).

six of six patients continued to have normal (unchanged) MR imaging studies. Representative imaging results are shown in Figure 1. At an MR imaging study 2 months after HDC/AHPCS, one of the three patients was seen to have bilateral T2-hyperintense white matter changes (Fig 1). At 3 months and beyond HDC/AHPCS, three (75%) of the four patients remaining in the study showed an increasing volume of white matter change. From 6 months to about 1 year after completion of HDC/AHPCS, the volume of abnormal white matter, by visual criteria, appeared to stabilize in the three patients with abnormalities.

The volumetric results for the four subjects studied beyond HDC/AHPCS are summarized in Figure 2. The volumetric analyses confirmed the visual impression of nonprogression of lesion volume beyond about 7 months after HDC/AHPCS, with maximal volumes of white matter calculated at 73, 151, and 166 cm^3.

MR Spectroscopy

Comparison of the mean MR spectroscopic ratio values for patients at each follow-up interval failed to show significant changes relative to entry values in any of the long-echo spectra for NAA/creatine (Cr), choline (Cho)/Cr, *myo*-inositol/Cr, and NAA/Cho, or for any of the short-echo spectra for NAA/Cho, *myo*-inositol/Cr, and NAA/Cho. At the time of the fifth MR imaging/MR spectroscopic study (at 6 to 10 months after HDC/AHPCS), there was an apparent decrease on short-echo spectra for NAA/Cr ($P = .03$, uncorrected for multiple analyses), and a decrease in Cho/Cr at the time of the sixth examination ($P = .03$, uncorrected for multiple analyses). Summary results plotted for the short-echo spectra in individual patients for the primary MR spectroscopic outcome measure, NAA/Cr, are shown in Figure 3. Despite the small sample size, there appeared to be a trend toward decreased ratios after HDC/AHPCS in three patients, including the patient whose MR imaging

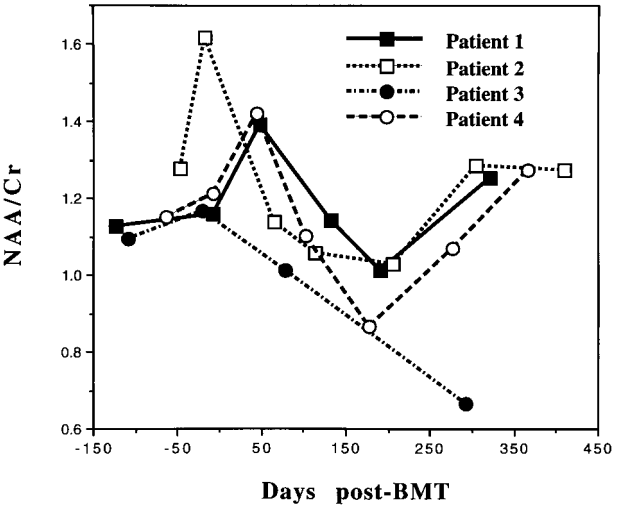

FIG 3. Serial NAA/Creatine (*Cr*) ratios. Single-voxel (8 cm^3) spectra were acquired using the stimulated-echo acquisition mode pulse sequence with a TR of 1600 and a mixing time of 13.7 milliseconds. Results are shown for the short-echo (TE = 30) spectra in the four patients studied after HDC/AHPCS (time 0).

studies remained normal. Two patients appeared to show a recovery of NAA/Cr to baseline levels on their late evaluations.

Discussion

The results of this prospective, longitudinal, pilot trial confirm our study hypothesis that severe white matter abnormalities are frequent sequelae of treatment of advanced breast carcinoma with HDC/AHPCS.

White matter abnormalities were identified in three of four patients studied beyond the conclusion of HDC/AHPCS therapy. This study design does not allow us to determine whether a longer delay after induction chemotherapy might be associated with white matter changes related to induction chemotherapy; however, it is unlikely that induction protocols alone would lead to extensive white matter changes, as these changes are not known to occur when similar induction protocols are used as components of other treatment trials. None of the patients in this or our previous studies (2, 3) was exposed to cranial X-radiation, therefore the most likely source of these white matter abnormalities is one or more of the combination chemotherapy agents used in this treatment protocol.

Although we were able to follow only a small study sample, we believe the patients studied beyond induction chemotherapy were representative. Even if the four study dropouts all had normal white matter at 1 year after HDC/AHPCS, the frequency of severe white matter changes we observed (38%) would have been important.

The MR imaging results indicate that white matter changes occur soon after conclusion of HDC/AHPCS treatment, at about 2 months. The imaging studies also showed that a rapid and progressive accumulation of white matter changes occurred up to about 6 months after HDC/AHPCS, and by imaging-based visual criteria and volumetric analyses, these white matter changes seemed to stabilize through the approximately 1-year post-HDC/AHPCS study interval. Previous retrospective studies have shown similarly large volumes of white matter change, up to 153 cm^3, in patients studied at intervals ranging from 14 to 21 months after HDC/AHPCS treatment, suggesting that many, if not all, of these changes are likely to be long-standing or permanent.

Despite these striking imaging changes, including nearly confluent white matter T2 hyperintensities, none of the patients showed persistent central neurologic symptoms. One patient with white matter changes did incur a chronic vestibular toxicity, and another patient without white matter changes contracted persistent tinnitus. Transient neurologic events were observed in two patients, including numbness in one patient with a persistently normal MR imaging study, and hemianopsia-aphasia in another patient with extensive white matter changes. One patient had an episode of visual disturbance. Ocular toxicity with variable degrees of vision loss and ischemic microvascular lesions of the retina and/or optic disc have recently been described in these patients (D. W. Johnson, personal communication, July 1997). Patients in this study were examined with a battery of neuropsychological measurements, but intersubject and intrasubject variation and potential learning effects were believed to preclude formal assessment of the results, given the small sample size. In this and previous studies, observations of transient deficits in short-term memory and other cognitive dysfunction have not been infrequent (A. Futterman and T. Simoneau, unpublished data, January 1997). A prospective study including neuropsychological and quality of life assessments is currently in progress.

Conventional spin-echo MR imaging sequences are believed to be highly sensitive to changes in the water spaces of the brain. The negative results from proton MR spectroscopic studies offer a very different perspective of HDC-induced white matter changes. This pilot study was designed to evaluate the potential of prospective, longitudinal, within-patient MR spectroscopic examination and to assess changes in the readily studied in vivo MR spectroscopic markers of brain function and disease. In particular, we were interested in NAA utilization to ascertain neuronal loss or dysfunction. For this pilot series of MR spectroscopic data, with the small number of subjects completing the protocol, we were unable to detect significant group or within-patient changes. However, the results did suggest that a decrease in NAA/Cr may accompany the early stages after HDC/AHPCS therapy at a time of maximal evolution of white matter change and , unlike MR imaging findings, may return to normal. These findings, however, require verification in a formal trial.

Conclusion

This prospective, longitudinal pilot trial suggests that white matter changes are common sequelae of HDC/AHPCS therapy and that the MR imaging-detected changes may stabilize by 6 months to 1 year after treatment. As in previous studies, the MR spectroscopic results suggest that neuronal damage or dysfunction is most likely limited and probably transient. MR imaging–based criteria alone would have been interpreted as suggesting that this chemotherapy results in massive and presumably important damage to the bulk of the white matter. However, taken together, these findings suggest that the effect of HDC may be predominantly on the water spaces of the white matter, which might explain the limited clinical dysfunction observed in these patients.

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