

CHANGES IN ^{87m}Sr CONCENTRATIONS IN SKELETAL METASTASES IN PATIENTS RESPONDING TO CYCLICAL COMBINATION CHEMOTHERAPY FOR ADVANCED BREAST CANCER

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Serial ^{87m}Sr bone scintigrams were performed on a series of patients being treated by cyclical combination chemotherapy for metastatic breast cancer. All the patients investigated responded to the chemotherapy, but initially the scintigrams showed an apparent deterioration, in that the tumor-to-normal isotope uptake ratios increased. Following this initial "flare" the scintigram appearance improved with a decrease in the tumor-to-normal uptake ratio. It is suggested that deterioration in the scintigram in the early stages of treatment should not be regarded as an indication that the patient is failing to respond.

The inadequacies of radiologic and biochemical techniques for the assessment of response to therapy in patients with osseous metastases from primary breast carcinoma are well recognized (1,2). Serial bone scintigraphy has been proposed by several workers as a potentially useful procedure in the management of such patients. However, the work published on this subject has not yet clarified the type of scintigraphic changes to be expected in the responding patient.

Galasko and Doyle (3) found in a small series that patients considered to be responding clinically exhibited ^{18}F scintigrams that qualitatively reverted towards normality. The treatment these patients received was not specified and the interval between the two scans was 3 months. Castronovo, Potsaid, and Pendergrass (4) presented a patient with bony metastases from lung carcinoma in whom the ^{99m}Tc -diphosphonate tumor-to-normal uptake ratios de-

creased after an 18-day course of x-ray therapy in two out of three metastatic areas studied. The authors do not state whether the patient was considered by other criteria to have responded. Kampffmeyer, et al (5) found no change in the ^{18}F scintigrams in five patients where hormonal treatment or chemotherapy produced regression of osseous metastases.

Greenberg, Chu, Dwyer, et al (6) using ^{47}Ca found that the majority of their series of nine patients exhibited a rise in isotope uptake by tumor-involved bone during the 1-2-month period after radiation therapy, followed by a gradual fall. These patients were considered by other criteria to have benefited from treatment. It is clearly important to ascertain whether or not the temporary increase in isotope concentration occurs in most responding patients. Recognition of this "flare" phenomenon would not only prevent misinterpretation of the scintigram but could be useful as an early indication of patient response.

We present here a small series treated by a cyclical combination chemotherapy regime on whom serial ^{87m}Sr scans were performed before and during therapy. The patients' response to treatment was objectively assessed and an attempt has been made to correlate disease remission or progression with changes in the appearance of the skeletal scintigram.

PATIENTS AND METHODS

The patients included in this series all suffered from advanced breast cancer with skeletal second-

Received June 4, 1974; revision accepted Oct. 15, 1974.

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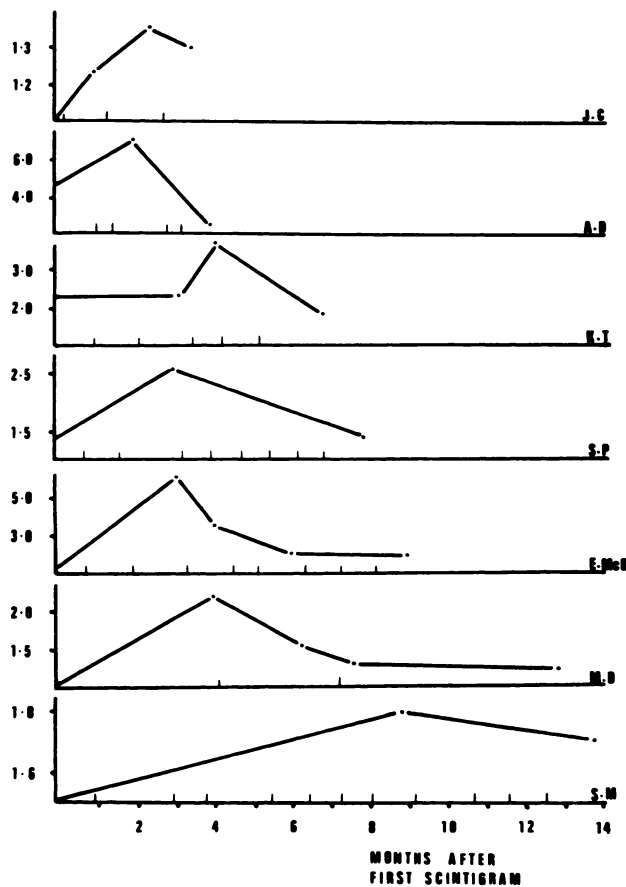


FIG. 1. Variation in tumor-to-normal ^{87m}Sr uptake ratios in skeletal metastases of patients responding to cyclical combination chemotherapy for advanced breast cancer. Chemotherapy courses are marked on abscissas.

aries in the dorsal spine, lumbar spine, or pelvis, confirmed both radiologically and by ^{87m}Sr scintigraphy. Treatment was by a combination chemotherapy regime utilizing endoxana, 5-fluorouracil, vincristine, and methotrexate (7). The dosage scheme was not identical for all patients, the quantity of each agent administered during successive treatment courses being in some cases modified by the patients' tolerance of the undesirable side effects. The intervals between courses and the temporal relationships between chemotherapy courses and scintigraphic investigations are illustrated in Fig. 1.

The ^{87m}Sr uptake ratios were determined 4 hr postinjection immediately after each scintigraphic examination using a Picker 500 Magnascanner and a No. 2112 collimator. The analyzer was set to accept the ^{87m}Sr photopeak and extreme care was taken to ensure identical geometry on each occasion by using an audio signal to center over the "hottest" region of the tumor, the collimator being positioned perpendicular to the spine at a fixed collimator-skin distance. Where multiple scintigraphic abnormalities were evident, the most abnormal region was chosen

to compare with normal bone. The area selected as normal was, if possible, a contralateral region showing no scintigraphic or radiologic abnormality; in the spine a vertebral body distant from the metastatic site was selected. Although it is recognized that lack of radiologic evidence of metastatic involvement does not definitely preclude the existence of a tumor, it did enable this and other conditions that can produce an enhanced ^{87m}Sr uptake to be excluded as far as possible. Little is known about the type of scintigraphic change that may occur following therapy and even less about the time required for changes to occur. This element, though possibly critical in the design of the experiment if short-term changes occur, must be selected arbitrarily.

We have attempted, with only moderate success due to difficulties in ensuring out-patient attendance etc., to carry out the scintigraphic investigations immediately before and halfway between each 5-week chemotherapy course. Each short vertical line on the abscissas of Fig. 1 indicates a chemotherapy course.

The classification of patients as responders required objective improvement of at least 50% in demonstrable lesions except bony deposits where the arrest of existing disease with pronounced subjective benefit is considered to be a response. Justification for this exception was considered to be the common and lasting relief of bone pain that occurs in the absence of radiologically demonstrable repair. A minimum of 10 weeks of sustained response is required and deterioration of any lesion or appearance of a new deposit is classified as failure.

RESULTS AND DISCUSSION

The seven patients on whom serial tumor-to-normal ^{87m}Sr uptake ratios were obtained were all classified by an independent assessor as responders. The variation of the ratios with time is illustrated in Fig. 1. The actual ratios and the changes in these following treatment varied considerably as inspection of the ordinates of Fig. 1 will show. Patient MD was exceptional in that she had a 5-day course of 2,500 rads ^{60}Co radiation to her spinal metastasis 4 weeks after the first scintigram was performed before chemotherapy was commenced. It appears from these results that an increase in ^{87m}Sr uptake in osseous metastases followed by a decrease may be expected in the responding patient. The fact that no nonresponding patients are in this small series precludes any valid statement regarding this rise and fall of ratio as a prognostic indicator.

The point we wish to stress is that this so-called flare phenomenon does exist and that an apparently

deteriorating ^{87}mSr scan is not an adequate basis on which to terminate a particular therapeutic regime.

The availability of $^{99\text{m}}\text{Tc}$ -labeled 1-hydroxy-ethylidene-1, 1-di-sodium phosphonate (HEDP) with its marked advantages over ^{87}mSr as an effective bone-scanning agent resulted in the above series being terminated after a relatively small number of patients was investigated.

We have recommenced the investigation using HEDP labeled with $^{99\text{m}}\text{Tc}$ and anticipate having results from 100 patients in about 1 year's time. The series should contain about 30 chemotherapy failures on current response rates and it may therefore be possible to relate early changes in scan appearance to subsequent response or failure.

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