Bone Scan Flare Predicts Successful Systemic Therapy for Bone Metastases

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Changes in osteoblast function, assessed by serial bone scans and serum alkaline phosphatase bone isoenzyme (ALP-BI) and osteocalcin, have been studied in 53 patients receiving systemic therapy for bone metastases from advanced breast cancer. In 12/16 patients with healing of lytic disease on x-ray a paradoxical deterioration in the bone scan appearances after 3 mo treatment was seen. This was characterized by increased activity in baseline lesions and the appearance of new foci of tracer uptake; changes which are indistinguishable from progressive disease. After 6 mo successful treatment the bone scan improved with reduced tracer uptake and no new lesions since the 3-mo scan. New lesions appearing after 6 mo indicated progressive disease. These changes are attributed to a flare in osteoblast activity induced by successful systemic therapy and confirmed by a transient rise in osteocalcin and ALP-BI. After 1 mo of treatment 15/16 responders showed a rise in both parameters compared with only 5/23 nonresponders ($p=<0.001$). The flare response is the rule rather than the exception after successful systemic therapy for bone metastases. The appearance of new lesions or increasing activity in known lesions during the first 3 mo is as likely to herald radiological response as disease progression.

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Bone metastases are a major clinical problem, especially in breast cancer, where bone is a frequent site of metastatic spread (*1*). Pain, hypercalcemia, pathologic fracture, and leucoerythroblastic anemia are common complications.

Remissions are frequent following endocrine and cytotoxic therapy with a median survival from the time of diagnosis of skeletal metastases of 20 mo (*2*). However, assessment of objective response in bone to systemic therapy is difficult and the true response rate is probably underestimated (*3*) by the UICC criteria (*4*) which require radiologic evidence of sclerosis in previously lytic lesions. Radiologic evidence of healing may not be visible for 6 mo or more and many patients will have apparently static disease on plain radiographs (*2*). New methods of assessing response have been suggested including biochemical markers of bone metabolism, alkaline phosphatase (ALP) (*5*), urinary calcium (*6*) and hydroxyproline excretion (*7*), carcino-embryonic antigen (*8*), and radionuclide bone scanning (*9*).

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Bone healing is mediated by osteoblasts and an early increase in osteoblast activity following successful systemic therapy has been observed as evidenced by a rise in ALP (*5*) and increased tracer uptake on the bone scan (*10,11*). We have studied prospectively patients with advanced breast cancer and bone metastases who are receiving systemic therapy. Changes in the bone scan appearances during therapy have been recorded and correlated with serial measurements of ALP bone isoenzyme (ALP-BI) activity and osteocalcin.

MATERIALS AND METHODS

Fifty-three women with advanced breast cancer and bone metastases, median age 58 yr (range 32–82 yr) were studied. All had radiologically confirmed progressive lytic bone metastases. In 22 (42%) patients, metastatic spread was clinically confined to the skeleton. Metastatic spread in the other 31 patients was to all common sites including liver and lung. No attempt was made to select patients on any particular therapy resulting in a diversity of systemic treatments. Twenty-six patients received an endocrine treatment and 27 chemotherapy.

Bone scans, with plain radiographs of abnormal areas, were

performed before treatment and repeated every 3 mo. Standard overlapping views were taken 3–4 hr after injection of 500 MBq of technetium-99m-labeled methylene diphosphonate.

Osteocalcin and ALP-BI are indirect markers of osteoblast activity. Osteocalcin is a small protein, unique to bone and tooth dentine, synthesized in osteoblasts and, once secreted, binds strongly to hydroxyapatite. The small fraction of the newly-synthesized protein, which fails to bind to hydroxyapatite spills over into the circulation (*12*). Serum levels are measured by radioimmunoassay and reflect new bone formation; raised levels are seen in conditions characterized by increased bone turnover including metastatic bone disease (*13*). Serum for measurement of osteocalcin and ALP-BI was obtained from a morning blood sample following centrifugation. All samples were frozen within 6 hr and stored at −20°C. Osteocalcin and ALP-BI were measured before and 1 mo after starting therapy. Subsequent measurements of osteocalcin and ALP-BI were made monthly and 3 monthly, respectively, until radiologic evidence of progressive disease occurred. Osteocalcin was measured by radioimmunoassay (Immuno Nuclear RIA) (*13*) and ALP isoenzymes by the modified heat-inactivation technique described by Moss (*14*).

The UICC criteria of response were used to assess the results of treatment (*4*). Radiologic evidence of healing with sclerosis of lytic metastases was necessary for a patient to be termed a "responder". In this study, the response category "no change" denoted stabilization of bone disease for a minimum of 12 wk. Changes in the bone scan appearances and biochemistry were compared with the UICC response achieved.

RESULTS

The UICC response categories in the 53 patients were a partial response (PR) with sclerosis of lytic areas in 16, no change (NC) in radiologic appearances over at least 3 mo in 14, and progression (PD) in 23. No patient achieved a complete response. The median duration of response was 12 mo (range 5–27+ mo).

The pre-treatment bone scans showed multiple sites of abnormal tracer uptake in all patients. Three months after starting treatment a repeat bone scan could not identify or predict response to therapy (Table 1). In 12/16 responding patients the 3-mo scan showed increased activity in baseline lesions and the appearance of new lesions suggesting, erroneously, progressive disease. In two patients the 3-mo bone scan was unchanged from baseline. Improvement in the bone scan appearances, with reduced activity in baseline lesions and no new areas of tracer uptake, was seen in only one responding patient.

In ten patients with progressive disease the bone scan appearances at 3 mo deteriorated with new lesions and/or increased activity in baseline lesions—appearances which were indistinguishable from those seen in responding patients. A further confounding feature in one patient was a reduction in uptake at sites of rapidly progressive lytic disease.

In 14/16 responding patients a repeat bone scan after 6 mo treatment showed improvement when compared with the one performed after 3 mo and was unchanged in the other two. Improvement was most marked in the 12 patients whose 3-mo scans had shown a deterioration from baseline. New lesions appearing after 6 mo reflected progressive disease or a fracture site.

The deterioration followed by subsequent improvement in the bone scan appearances following successful therapy corresponds to a transient increase in osteoblast activity during the early phase of healing and is termed

TABLE 1
Changes in the Bone Scan Appearances 3 mo After a Change in Systemic Therapy

Bone scan appearances		UICC Response category PR (n = 16)	NC (n = 14)	PD (n = 23)
Number of lesions:	Increased	12	2	9
	Unchanged	4	10	5
	Reduced	0	0	0
Activity of lesions:	Increased	12	2	10
	Unchanged	2	5	3
	Reduced	1	4	1
	Mixed change*	1	1	0
	Other	0	1†	0
Increase in activity and number of lesions:		12	2	9
No change in activity or number of lesions:		2	5	2
Scan not repeated:		0	1	9

* Activity increased in some lesions and reduced in others.
† Diffuse increased activity (superscan) became more focal.
PR = partial response, NC = no change, PD = progressive disease

the flare response. Illustrative examples are given in Figures 1–3.

The biochemical markers of osteoblast activity similarly show a flare during the early phase of healing. Figure 4 shows the serial ALP-BI and Figure 5 the serial osteocalcin measurements. The median percentage change from baseline is plotted. After 1 mo of systemic therapy all responding patients showed a >10% rise in ALP-BI (mean increase 233 IU/l, median 148 IU/l) and 15/16 a >0.5ng/ml rise in osteocalcin (mean increase 2.1 ng/ml, median 2.3 ng/ml). Figure 6 shows the baseline and 1-mo values of ALP-BI and osteocalcin in the 16 responders. The early increase in osteoblast activity seen in responding patients was followed by a gradual decrease over subsequent months as the response continued and re-mineralization occurred.

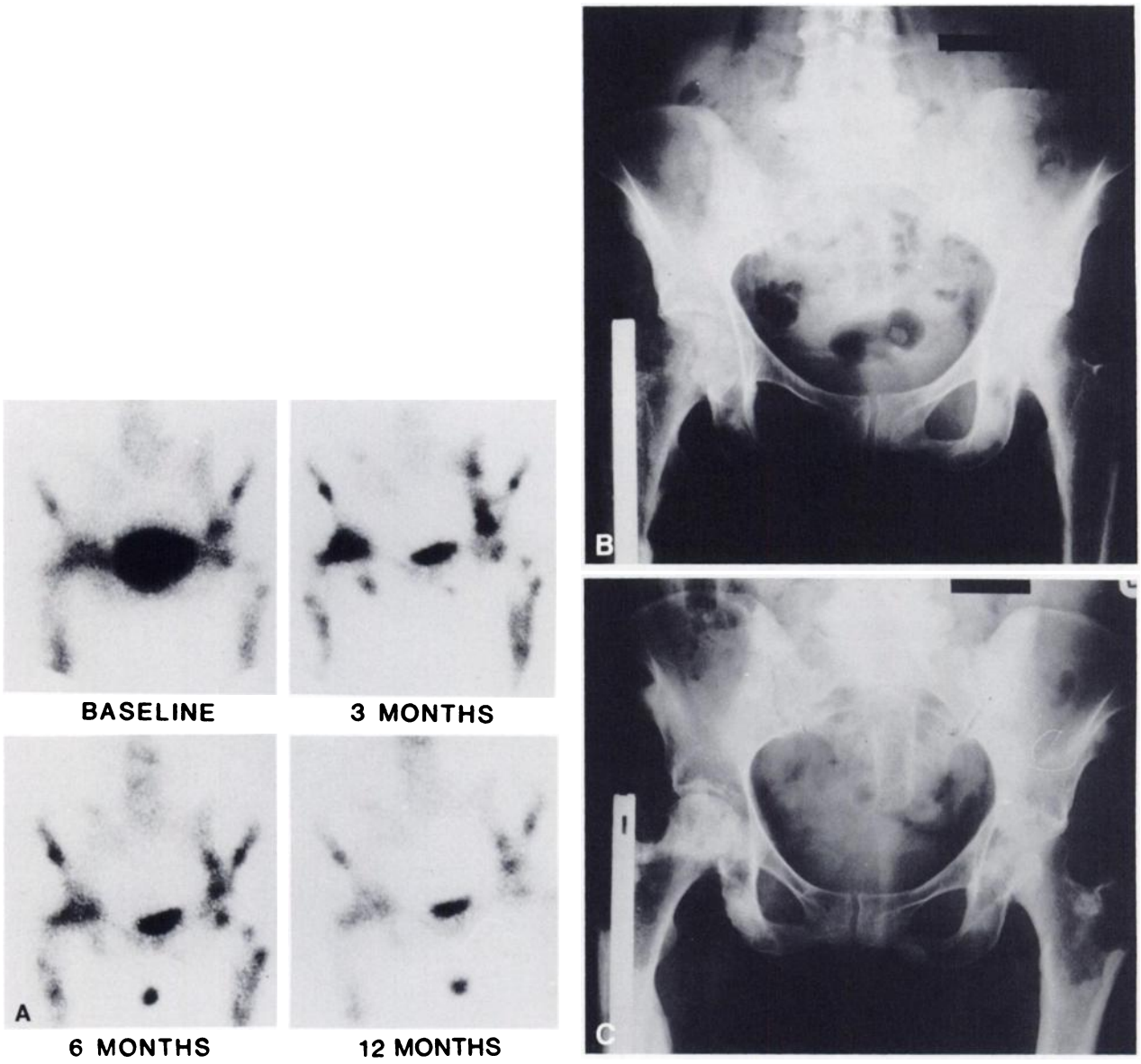

FIGURE 1
Serial bone scans of a patient responding to endocrine therapy with tamoxifen and prednisolone to illustrate the flare response. The baseline, 3, 6, and 12 mo bone scans are shown in (A). Increased activity in baseline lesions and new scan lesions are seen at 3 mo followed by improvement at 6 and 12 mo. Radiographs of the pelvis before (B) and 6 mo after starting treatment confirm response with sclerosis of lytic disease (C).

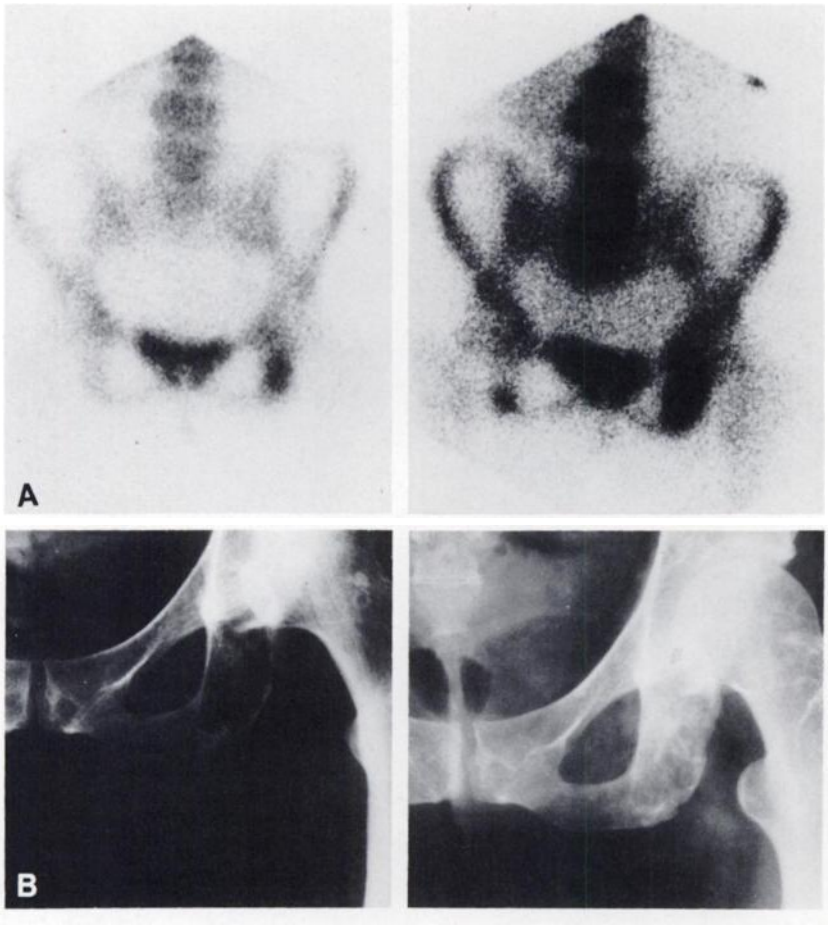

FIGURE 2
Bone scans performed before and 3 mo after starting treatment with chemotherapy (cyclophosphamide, methotrexate and 5 flurouracil) (A). A new lesion is seen in the left ischium on the bone scan. Plain radiographs (B) show that sclerosis has occurred in this area.

Changes in ALP and osteocalcin were variable and usually small in patients with progressive disease. Only 5/23 of this group had a >10% rise in ALP-BI and a >0.5 ng/ml rise in osteocalcin compared with 15/16 responders ($p=<0.001$). Patients with static disease on x-ray showed little change at 1 mo in ALP-BI (mean +23 IU/l, median −25 IU/l) and a moderate increase in osteocalcin (mean 1.9 ng/ml, median 1.4 ng/ml).

DISCUSSION

Bone destruction from metastatic disease is mediated by osteoclasts which are stimulated by paracrine factors secreted by malignant cells in the marrow cavity (*15*). In lytic metastases the normal coupling between osteoblast and osteoclast function is disturbed and bone resorption predominates. Control of the tumor, by systemic therapy, reduces osteoclast activity and allows bone healing to occur. This study has shown how osteoblast activity rapidly increases after the initiation of successful therapy for lytic bone metastases.

Serial bone scans were difficult to interpret. Deterioration in the bone scan appearances after 3 mo treatment initially led the nuclear medicine consultant to report progressive disease in 12/16 patients who subsequently showed radiologic evidence of bone healing. This flare response cannot be distinguished from progressive disease. New bone scan lesions may appear during the early months of successful therapy and represent healing in lesions either too small to be detectable or failing to promote a discernible osteoblastic response. Subsequent improvement after 6 mo treatment was seen although the bone scan remained abnormal in all patients in this study. New lesions appearing after 6 months of therapy indicated progressive disease or a site of fracture.

Bone scanning in advanced disease should be interpreted with caution within 6 mo of a change in therapy. In these circumstances bone scanning is most useful for re-staging at the time of relapse to identify sites for radiologic assessment and possible sites at risk of pathologic fracture.

Serial biochemical measurements of osteoblast function confirmed the flare response. Fifteen of sixteen patients with radiologic evidence of response had a rise in both ALP-BI and osteocalcin measurements. After a peak at 1–2 mo, both parameters fall as the response continues. The fall in osteocalcin occurs more slowly reflecting continuing re-mineralization.

The flare in osteoblast activity has been noted previ-

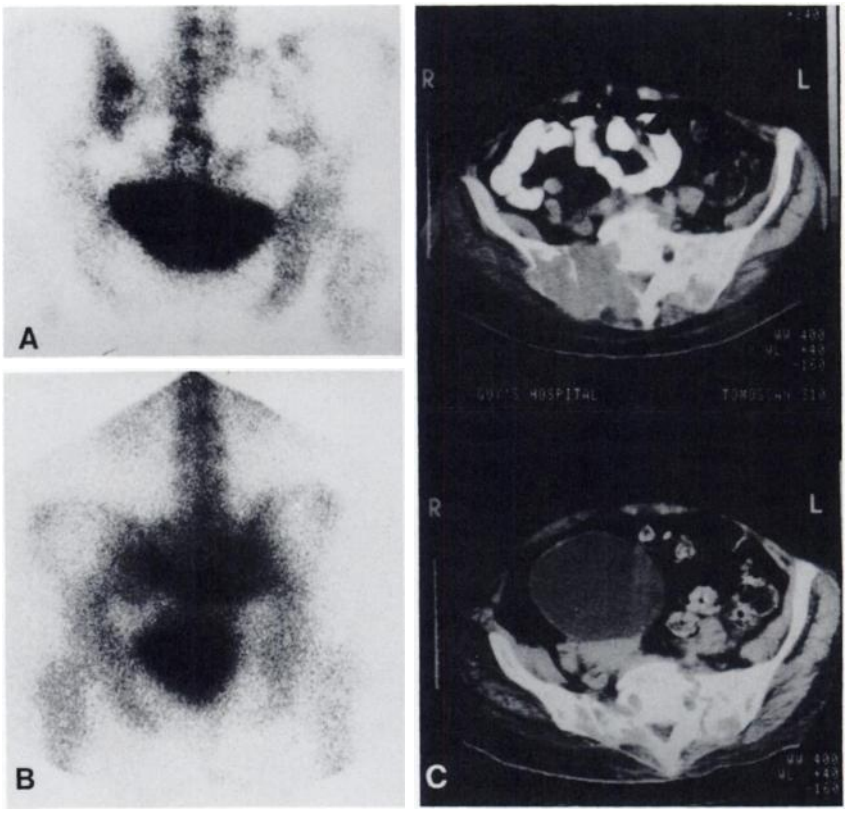

FIGURE 3
Extreme example of the flare response. Photon deficient lesions in sacrum on baseline scan (A) become "hot" as healing occurs in response to chemotherapy with adriamycin (B). CT sections confirm healing with sclerosis of bone and resolution of the soft-tissue component (C).

ously (*5,11*) but has not been prospectively evaluated in a large number of patients. In this study the biochemical flare was a sensitive predictor of subsequent radiologic response. Useful clinical information is available to the physician after only 1 mo of therapy, long before radiological evidence of response can be expected. The presence of a flare should encourage the clinician to continue with therapy.

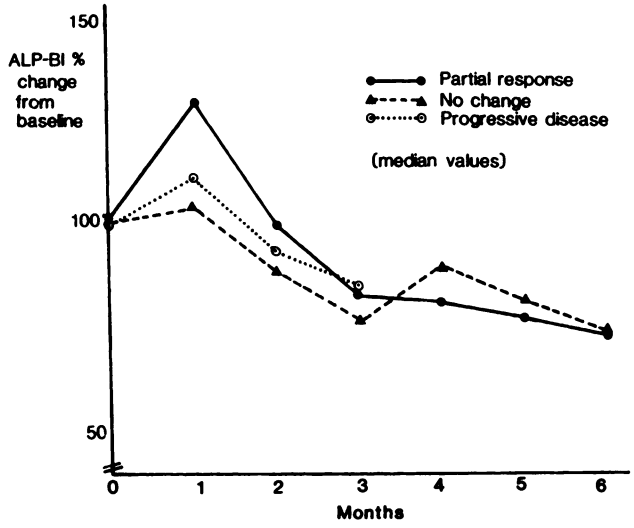

FIGURE 4
Serial changes in ALP-BI during systemic therapy. Data presented as % change from baseline for each UICC response group. Points represent median values. Baseline = 100%.

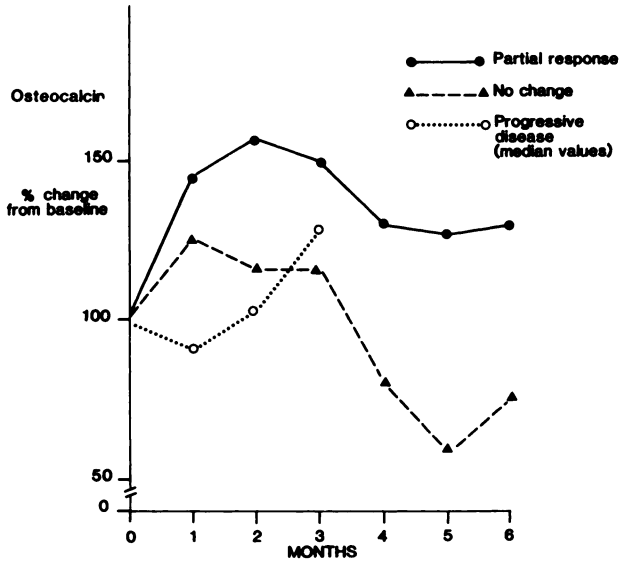

FIGURE 5
Serial changes in osteocalcin. Data presented as in Figure 4.

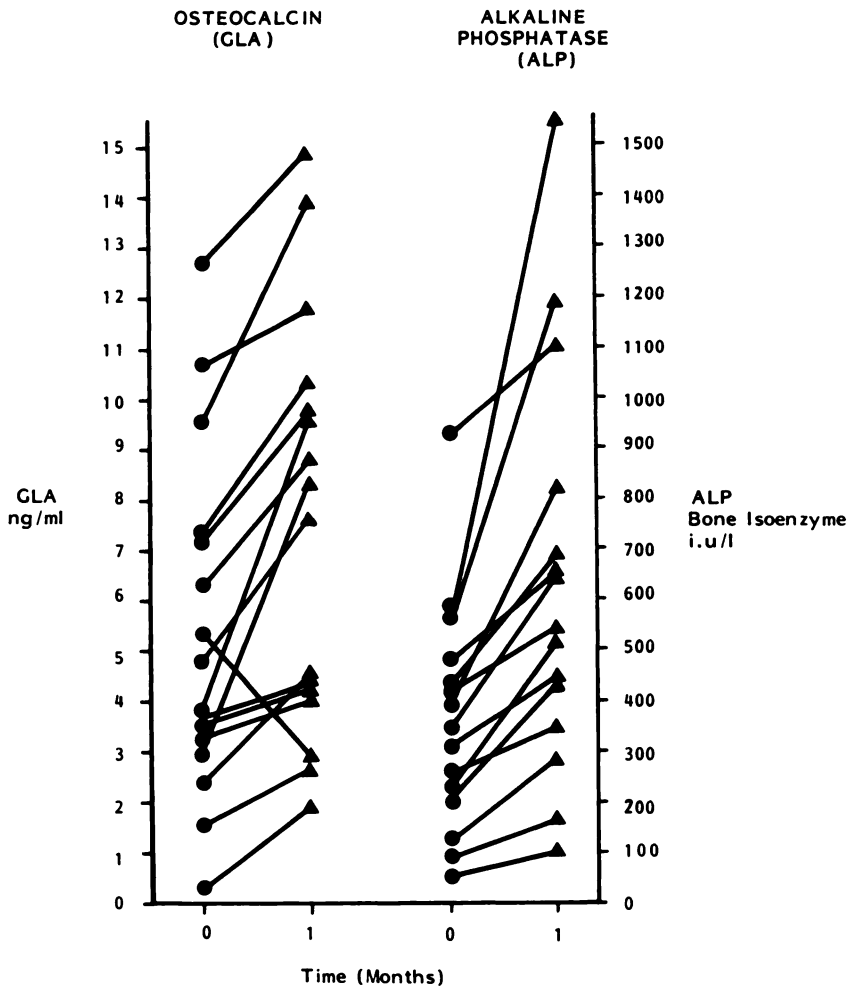

FIGURE 6
Osteocalcin and ALP-BI levels before and 1 mo after successful systemic therapy (individual values in responding patients).

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