Flare on Bone Scintigraphy Following Taxol Chemotherapy for Metastatic Breast Cancer

Jesse A. Schneider, Chaitanya R. Divgi, Andrew M. Scott, Homer A. Macapinlac, Andrew D. Seidman, Stanley J. Goldsmith and Steven M. Larson*

The Nuclear Medicine Service and Solid Tumor Service, Memorial Sloan-Kettering Cancer Center, New York, New York

Our goal was to determine if a healing flare response seen on bone scintigraphy occurs following chemotherapy with Taxol (paclitaxel; Bristol-Myers Squibb Co, Princeton, NJ), a novel antimicrotubule agent for metastatic breast cancer. **Methods:** We performed 74 bone scans on 21 females with breast cancer and bone metastases entering a Phase II trial of Taxol chemotherapy with granulocyte colony stimulating factor (G-CSF). All patients had baseline scans within 6 wk prior to therapy, after the second cycle (4–6 wk) of Taxol, and then after 6–12 mo. All bone scans were reviewed by two nuclear medicine physicians, without knowledge of the patients' clinical history. Skeletal radiographs, CT and MRI scans, as well as clinical history were compared with scan findings. **Results:** Seven of the 21 patients showed improvement in bone scan findings. Of these seven, three had a flare response following two cycles (4–6 wk) of Taxol, characterized by increased activity in baseline lesions and the appearance of new lesions, followed by improvement on follow-up scans. Evidence of clinical response (≥50% reduction in tumor mass) was seen in all of these patients. Seven patients showed no change in baseline findings on follow-up bone scans. Seven patients had post-Taxol scans showing new lesions, with no overall improvement on later follow-up. **Conclusion:** Flare on bone scintigraphy may be seen shortly after commencing Taxol chemotherapy. Bone scans done within the first 3 mo must be interpreted with caution and should be correlated with clinical and radiological findings to avoid inappropriate discontinuation of Taxol chemotherapy.

Key Words: Taxol; flare; bone scintigraphy; breast cancer

J Nucl Med 1994; 35:1748–1752

Bone scintigraphy is an effective modality in the detection of skeletal metastasis from breast cancer, frequently providing the first evidence of distant malignant spread. It has been shown to be more sensitive in detecting skeletal metastatic disease in breast cancer than the radiographic skeletal survey (*1,2*). Bone scan findings, however, are nonspecific, with areas of abnormally increased uptake probably reflecting osteoblastic activity and change in blood flow. In lytic metastases, bone destruction is mediated by osteoclasts. These are stimulated by paracrine factors secreted by malignant cells in the marrow cavity, resulting in an imbalance between osteoblast and osteoclast function. Bone resorption then predominates. Osteoclast activity is reduced as the tumor is controlled by therapy and bone healing follows (*3*). Biochemical markers of osteoblast activity including osteocalcin and alkaline phosphatase may show a transient increase or flare response with successful systemic chemotherapy and hormonal therapy (*3,4*). It has been hypothesized that scintigraphic flare may represent this increased osteoblast activity. It may also reflect increased blood flow due to an inflammatory response at sites of skeletal tumor destruction (*5*). Alternatively, with endocrine therapy, flare may be due to increased osteoblast activity in response to transient hormonal stimulation of tumor growth (*6*). The flare response, characterized by an increase in number and intensity of focal osseous lesions on bone scan, followed by a subsequent corresponding decrease, has long been recognized as occurring shortly after starting hormonal and cytotoxic chemotherapy (*2–4,6–10*). The recognition of the possibility of a flare response at the commencement of therapy is essential since it warrants continuation of therapy. We undertook this study to determine if flare on bone scintigraphy occurs following treatment with Taxol, a new anti-microtubule chemotherapy agent used in combination with recombinant human granulocyte colony stimulating factor (G-CSF) in a Phase II trial in females with metastatic breast carcinoma at Memorial Sloan-Kettering Cancer Center.

MATERIALS AND METHODS

A Phase II trial of Taxol systemic chemotherapy used in combination with G-CSF was conducted at Memorial Sloan-Kettering Cancer Center in females with histologically confirmed advanced (Stage IV) adenocarcinoma of the breast. Twenty-one females in this trial, median age 47 yr (range 32–62 yr), were followed during and after treatment with serial bone scans. A total of 74 bone scans were obtained from these patients. All patients had pretreatment scans showing bone metastases. Baseline scans were performed within 6 wk prior to therapy, after the second cycle (4–6 wk) of Taxol, and then after 6–12 mo.

Fourteen patients had various pre-Taxol treatment regimens including adjuvant chemotherapy or chemotherapy for advanced

Received Nov. 30, 1993; revision accepted June 23, 1994.

For correspondence and reprints contact: Chaitanya R. Divgi, MD, Nuclear Medicine Service H213, MSKCC, New York, NY 10021.

*Peer and editorial review were conducted by R. Edward Coleman, MD, Associate Editor, Duke University Medical Center, Durham, NC.

disease. The remainder had no prior chemotherapy. Most patients had received prior exogenous hormone therapy or radiation therapy (to less than 30% of the marrow bearing bone). After premedication with a standard regimen of 20 mg of oral dexamethasone 12 and 6 hr before Taxol, 50 mg of diphenhydramine HCL intravenously and 300 mg of cimetedine intravenously 1 hr before Taxol, patients received 200–250 mg/m^2 of Taxol intravenously by continuous infusion over 24 hr every 21 days. G-CSF 5 μg/kg/day was administered subcutaneously on days 3–10 (8 days in all). Patient 15 did not receive G-CSF.

Bone scans were performed following injection of 925 MBq (25 mCi) of ^{99m}Tc-methylene diphosphonate (MDP). All patients were scanned between 2 and 3 hr after the administration of the radiopharmaceutical. Whole-body scans (anterior and posterior views) were obtained with a gamma camera (ADAC Inc., Milpitas, CA) equipped with a low-energy, high-resolution collimator, interfaced to a dedicated Pegasys computer system. Supplemental additional planar views and SPECT scans were obtained when necessary.

All scans were reviewed independently by two nuclear medicine physicians without knowledge of the patients' clinical history who evaluated for the presence of abnormal sites of uptake and intensity of uptake (grade 1: slight, grade 2: moderate, grade 3: intense). Changes in overall scan appearance and individual sites of abnormal uptake were also evaluated in sequential studies of individual patients. Any disagreement between reviewers was resolved by consensus. Improvement in scan appearance was defined as a reduction in intensity of individual lesions by at least one grade or disappearance of abnormal sites of uptake. Worsening in scan appearance was defined as an increase in intensity by at least one grade or an increase in number of sites of abnormal uptake. "Flare" was defined as a worsening in bone scan appearance, coinciding with therapy, which showed substantial improvement in subsequent follow-up scans (*3*).

Skeletal radiographs, CT and MRI scans, as well as clinical history were all compared with bone scan findings.

RESULTS

Seven of the 21 patients showed improvement in bone scan findings by 6–12 mo after commencement of therapy, characterized by a decrease in the number or intensity of baseline lesions. Of these seven, three had a flare response seen on the first scan performed after commencing Taxol (2 cycles of Taxol; 4–6 wk), characterized by increased activity in baseline lesions and the appearance of new lesions, followed by subsequent improvement on follow-up scans. All of the patients showing flare had corresponding partial clinical responses, defined as a ≥50% decrease in measurable tumor mass. Two of the patients with flare had prior chemotherapy and one had external radiation therapy before initiation of Taxol. Patients showing improvement without flare had either minor responses in their index (nonosseous) lesions, defined as a decrease of less than 50% but more than 25% in tumor mass, or stable disease. Characteristics of patients showing improvement on bone scans are shown in Table 1.

Four weeks after commencing therapy (two cycles of Taxol), Patient 8 showed the appearance of multiple new lesions including a skull lesion, several ribs, several thoracolumbar vertebrae and a left femoral lesion, as well as worsening of a pelvic and a sternal lesion (Fig. 1). Sclerosis was seen in a previously lytic pelvic metastasis on CT scan 4 wk after commencing therapy (Fig. 2). Approximately 10 mo after commencing Taxol therapy, the scan appearance was markedly improved, showing interval disappearance of all new lesions and a return to baseline appearance or disappearance of other lesions. Patient 21 showed the appearance of multiple new lesions including a rib, shoulder girdle, thoracic spine, pelvis and right femur, as well as worsening of a cervical spine lesion after the second cycle of Taxol. Simultaneously, a partial response to Taxol was seen in a right breast mass. Follow-up scans showed improvement in all bony lesions (Fig. 3). Patient 1 showed an increase in intensity of uptake in several previously observed lesions in the spine and a rib, 4 wk after commencing therapy (two cycles of Taxol). A partial response to Taxol was observed in nonosseous sites, characterized by decrease in size of supraclavicular and mediastinal lymph nodes after two cycles of Taxol. After four cycles of Taxol, she was switched to Adriamycin. A follow-up bone scan done 4 mo after discontinuing Taxol showed interval disappearance of most of these lesions and improvement of a pelvic and a lumbar vertebral lesion.

Seven patients showed no change in baseline findings on follow-up scans, which corresponded to stable disease, minor responses, or partial responses in index (nonosseous) lesions. Seven other patients had post-Taxol scans showing the appearance of new lesions, with no overall improvement on later follow-up. Patient response index lesions in this group were: progression of disease in one, stable disease in one, minor response in two, and partial response in three patients. The correlation between bone scan findings and clinical responses in this group, therefore, was low.

DISCUSSION

Osseous metastases occur in the majority of patients with metastatic breast cancer, with bone being the most common site of metastasis found at autopsy (*8*). While clearly defined and reproducible criteria for evaluating response of osseous metastases to therapy do not yet exist, the bone scan is widely recognized as being useful in this setting. Scintigraphic flare responses have been well documented previously in patients with metastatic solid tumors, with a variety of cytotoxic agents and endocrine treatment. It has generally been seen between 3 to 6 mo after commencement of therapy, with subsequent improvement in bone scan findings within several months. Alexander et al. found flare in 11 of 18 patients with skeletal metastases from breast cancer shortly after commencing combination chemotherapy (*11*). Coleman et al. reported flare in 12 of 16 patients, 3 mo after receiving systemic chemotherapy for bone metastases from advanced breast cancer (*3*). Pollen et al. reported a series of 18 patients with objective clinical remission after chemotherapy or hormonal treatment of metastatic cancer of the

TABLE 1
Patient Characteristics and Response to Therapy

Patient	Age (yr)	Prior chemo*	Prior RT†	Sites of bony disease	Index lesion(s)	Response‡	Scan findings
1	60	Yes	Cervical spine	Ribs, spine, pelvis	(L) supraclavicular node	PR	Flare§
6	59	No	Right tibia	Spine, pelvis, extremities	Chest wall	MR	Improved, no flare
8	41	Yes	None	Skull, sternum, ribs, spine, pelvis, extremities	Pelvis	PR	Flare
9	34	Yes	None	Sternum, ribs, spine, shoulder	Scapula	SD	Improved, no flare
10	47	No	Ls¶ spine	Skull, sternum, ribs, spine, pelvis, extremities	Skull	SD	Improved, no flare
16	46	Yes	T3-11, right hip	Skull, spine, pelvis, extremities	Lung	SD	Improved, no flare
21	43	No	No	Ribs, spine, pelvis	Right breast mass	PR	Flare

*Chemo = chemotherapy, usually consisting of cytoxan, adriamycin and 5-FU.
†RT = radiation therapy.
‡Response: PR = partial response (≥50% reduction in index lesion size); MR = minor response (25%–50% reduction in index lesion size); SD = stable disease (no change in index lesion size).
§Flare: Increased activity in baseline lesions and/or appearance of new lesions, with improvement to or better than pre-Taxol appearance, on follow-up scans.
¶Ls = lumbosacral.

prostate, two showing flare on bone scan after 3 mo of therapy (*4*).

In a series of 26 patients with advanced prostate cancer, treated with the leutinizing hormone releasing hormone analog, leuprolide acetate, five patients had flare between 3 and 6 mo after initiation of therapy (*5*). In prostate carcinoma, the clinical response to endocrine treatment occurs often within a few days to a few weeks, therefore, a flare reaction on bone scan may occur much earlier than 3–6 mo (*9*). Cosolo et al. reported two cases of flare in patients treated with chemotherapy for small cell carcinoma of the lung, after three courses (3 mo) of chemotherapy (*10*).

Taxol is a novel anti-microtubule agent derived from the bark of the Pacific yew, Taxus brevifolia. Interest dates from the late 1960s when a crude extract was tested by the National Cancer Institute in a large-scale screening pro-

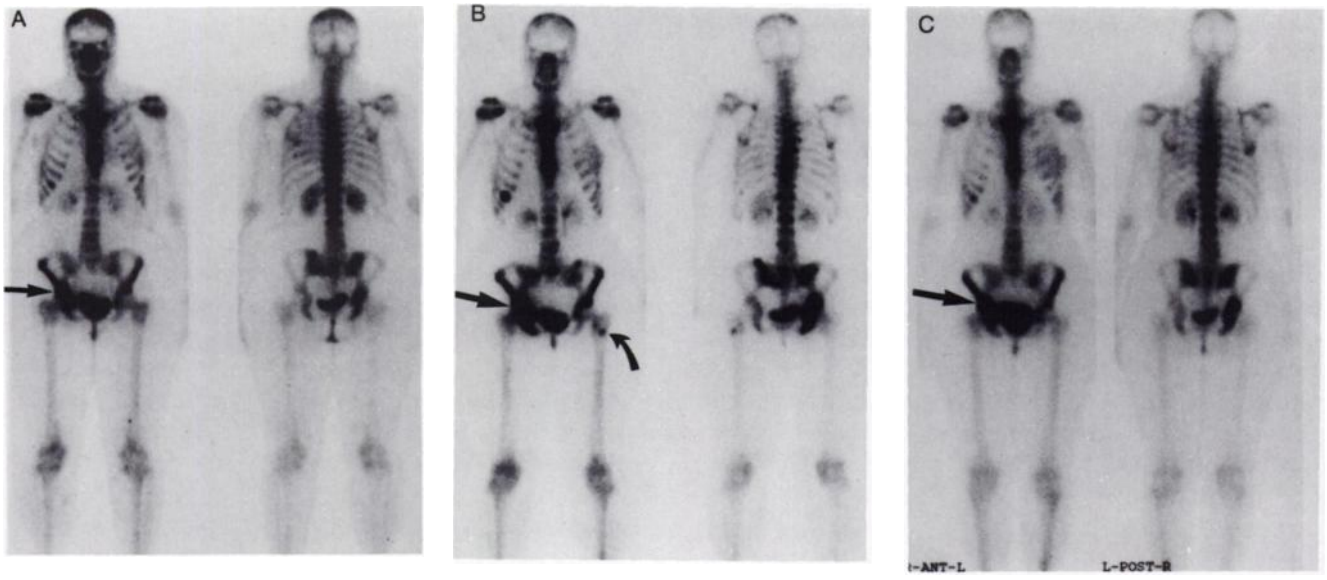

FIGURE 1. Serial bone scans in Patient 8 responding to Taxol illustrates the flare response. Bone scans at baseline (A), after two cycles of Taxol (B), and 10 mo after commencing therapy (C) are shown. New lesions (curved arrow in B) and increased activity in baseline lesions (straight arrows) are seen at 4 wk, followed by improvement 10 mo later.

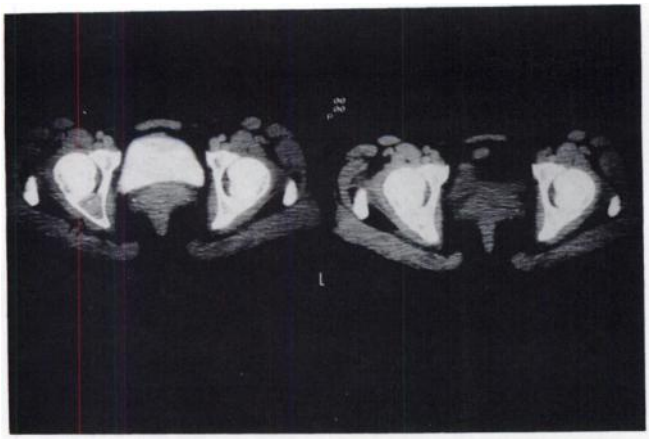

FIGURE 2. (Left) Initial pelvic CT (Patient 8) prior to therapy shows a lytic lesion (arrow) in the left ischium. (Right) Repeated pelvic CT, after the second cycle of Taxol demonstrates healing.

gram, demonstrating cytotoxic activity against several murine tumors. Despite its promising antitumor activity, development of Taxol as an antineoplastic agent was hampered by its scarcity and problems with preparation. Renewed interest in Taxol has been rekindled by the discovery of Taxol's unique cytotoxic mechanism as a stabilizer of microtubules against depolymerization. Extremely stable and nonfunctional microtubules are formed, resulting in growth inhibition and loss of cell viability. In contrast to Taxol, other microtubule toxins in clinical use, such as vincristine and colchicine, induce microtubule disassembly. Encouraging results with Taxol have been observed since clinical trials began in 1983. Responses have been seen in non-small cell lung cancer, refractory ovarian carcinomas, melanoma, head and neck cancer, gastric cancer, colon cancer and adenocarcinoma of unknown primary site (*13*). Two recently conducted Phase II clinical trials of Taxol in metastatic breast carcinoma demonstrate a high level of anti-tumor activity. The M.D. Anderson group reported an objective response rate of 56% (12% complete and 44% partial) (*13*). In the Memorial Sloan-Kettering Cancer Center trial of Taxol and recombinant human G-CsF a response rate of 62% (12% complete and 50% partial) was observed (*14,15*).

The observations in this report underline the importance of ascertaining the types of changes which might occur on bone scintigraphy during treatment with new cytotoxic agents. In three of 21 patients, worsening of bone scan appearance which involved increased uptake in baseline lesions, as well as the appearance of new lesions in the first month after therapy, was indistinguishable on a bone scan from disease progression. However, each of these patients had other objective evidence of response in the first few weeks after starting Taxol. Results of the long-term follow-up scans in one of these three patients was confounded by the chemotherapy with other agents she received following Taxol, however, the objective evidence of response during Taxol therapy suggests that the bone scan findings observed do represent flare in this patient, as well.

It is clear, therefore, that bone scans done within the first few months following Taxol chemotherapy showing "worsening" must be interpreted with caution and must be compared with clinical findings and other imaging modalities to avoid an erroneous impression of disease progression and unwarranted discontinuation of treatment. While soft-tissue masses with accurately measurable dimensions are easily followed by serial clinical evaluation or radiological studies, determining response to therapy of bony lesions by radiological studies is frequently difficult. Radiological changes in bone metastases typically occur very

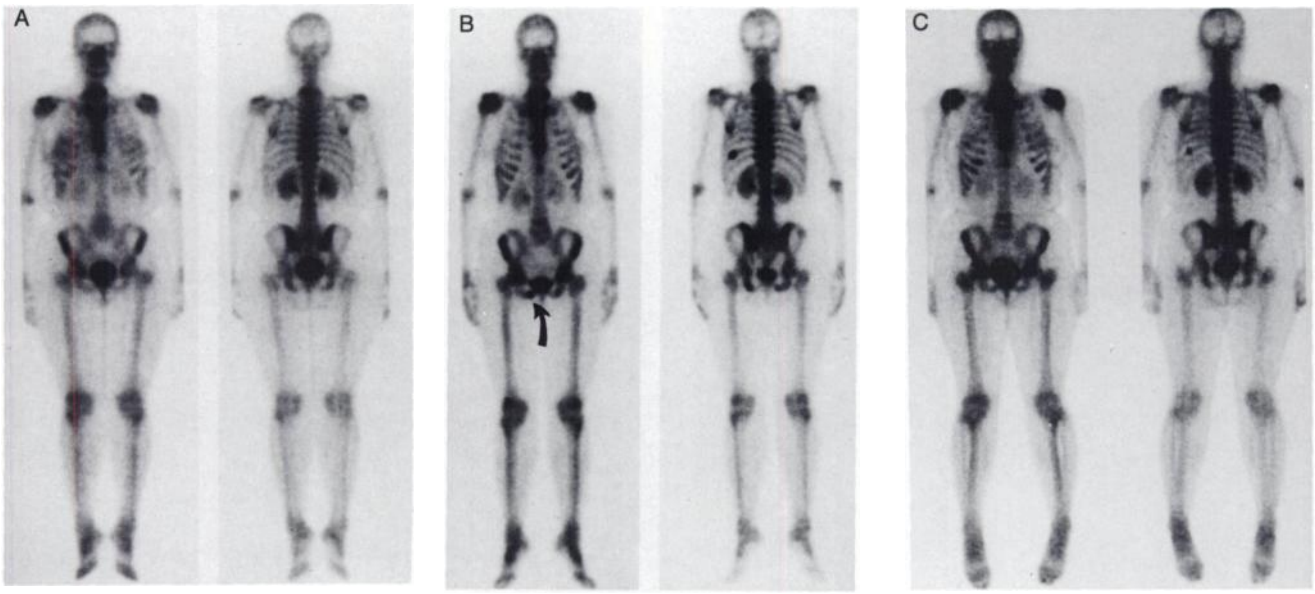

FIGURE 3. Serial bone scans in Patient 21 responding to Taxol illustrates the flare response. Bone scans at baseline (A), after two cycles of Taxol (B), and 12 mo after commencing therapy (C) are shown. New lesions (curved arrow in B) and increased activity in baseline lesions are seen at 4 wk, followed by improvement on follow-up.

slowly, generally over months, or not at all. Briton et al. found that skeletal radiographs only infrequently show objective improvement after treatment of metastatic breast cancer with chemotherapy, despite objective improvement in nonosseous metastases (*7*). Rossleigh et al. found that radiographs often do not show sclerosis of lytic lesions in breast cancer patients with flare (*8*). Radiological studies, therefore, may not resolve the dilemma of progression versus flare, and correlation with other clinical indicators of disease status is mandatory; a follow-up bone scan in approximately 3 mo is frequently necessary to differentiate between these etiologies. If a bone scan done shortly after commencing therapy shows apparent worsening, but there is no other corroborating evidence of disease progression, the clinician should consider a possible flare response and be encouraged to continue therapy. Recognition that a flare response may occur during the first months of Taxol chemotherapy for breast carcinoma should improve the interpretation of bone scintigraphy in these patients. Bone scans done several weeks after Taxol therapy may maximize the demonstration of bone metastases if a flare response is occurring. Although none of the patients with a flare response in our study had normal pre-treatment scans, a flare response in previously undetected bone lesions in a patient with a normal baseline bone scan seems possible, and its detection may lead to a change of clinical stage assignment and further evaluation in some cases. The bone scan, therefore, may provide useful clinical information and guide therapy after only 4–6 wk of therapy, long before radiological evidence of response can be expected, providing the flare response is recognized. We feel that bone scans carried out 3 mo or longer after the last dose of chemotherapy usually do not show any flare response, and that in order to assess disease progression or response on a bone scan, it is useful to wait for at least 3 mo from the last dose of chemotherapy. Additional study is needed to optimize the use and timing of bone scans in patients receiving Taxol.

One possible confounding factor in our observations was the use of G-CSF in these patients. The effect of G-CSF and related cytokines on bone scan findings after therapy is unclear. The possibility that G-CSF treatment may produce increased uptake in focal pre-existing lesions (or produce new focal areas of increased uptake) seems unlikely in view of the marrow-expanding effect of this agent. Diffuse increased uptake on bone scintigraphy in the axial skeleton and juxta-articular areas in addition to the flare response has recently been observed in patients receiving G-CSF in combination with systemic chemotherapy (*16*). Increased uptake in patients receiving these hematopoietic growth factors may be due to an increase in marrow cellularity. Diffusely increased skeletal uptake of ^{201}Tl-Cl has also been described in patients receiving G-CSF, thought to be due to hypermetabolic marrow secondary to G-CSF stimulation (*17*). Future studies are required to further clarify the spectrum of bone scan changes associated with cytokine therapy, particularly in view of the increased use of these agents in high-dose chemotherapy trials.

REFERENCES

1. Hortobagyi GN, Libshitz HI, Seabold JE. Osseous metastasis of breast cancer. chemical, biochemical, radiographic, and scintigraphic evaluation of response to therapy. *Cancer* 1984;53:577–582.
2. Citrin DL, Hougen C, Zweible W, et al. The use of serial bone scans in assessing response of bone metastases to systemic treatment. *Cancer* 1981; 47:680–685.
3. Coleman RE, Mashiter G, Whitaker KB, Moss DW, Rubens RD, Fogelman I. Bone scan flare predicts successful systemic therapy for bone metastases. *J Nucl Med* 1988;29:1354–1359.
4. Pollen JJ, Shlaer WJ. Osteoblastic response to successful treatment of metastatic cancer of the prostate. *AJR* 1979;132:927–931.
5. Johns WD, Garnick MB, Kaplan WD. Leuprolide therapy for prostate cancer: an association with scintigraphic "flare" on bone scan. *Clin Nucl Med* 1990;15:485–487.
6. Vogel CL, Sherman I, Reynolds R, Gams R. The "worsening" bone scan in breast cancer clinical trials: a potentially significant source of error in response evaluation [Abstract]. *Proceedings of Am Soc Clin Oncol* 1992; 11:A26.
7. Briton JA, Bekerman C, Desser RK. The predictive value of serial bone scans in assessing response to chemotherapy in advanced breast cancer. *Cancer* 1980;45:1562–1568.
8. Rossleigh MA, Lovegrove FT, Reynolds PM, Byrne MJ. Serial bone scans in the assessment of response to therapy in advanced breast carcinoma. *Clin Nucl Med* 1982;7:397–402.
9. Pollen JJ, Witztum KF, Ashburn WL. The flare phenomenon on radionuclide bone scan in metastatic prostate cancer. *AJR* 1984;142:773–776.
10. Cosolo W, Morstyn G, Arkles B, Zimet AS, Zalcberg JR. Flare response in small cell carcinoma of the lung. *Clin Nucl Med* 1988;13:13–16.
11. Alexander JL, Gillespie PJ, Edelstyn GA. Serial bone scanning using technetium-99m-diphosphonate in patients undergoing cyclic combination chemotherapy for advanced breast cancer. *Clin Nucl Med* 1976;1:13–17.
12. Rowinsky EK, Cazenave LA, Donehower RC. Taxol: a novel investigational antimicrotubule agent. *J Natl Cancer Inst* 1990;82:1247–1259.
13. Holmes FA, Walters RS, Theriault RL, et al. Phase II trial of Taxol, an active drug in the treatment of metastatic breast cancer. *J Natl Cancer Inst* 1991;83:1797–1805.
14. Reichman B, Seidman A, Crown J, et al. Paclitaxel and recombinant human granulocyte colony-stimulating factor as initial chemotherapy for metastatic breast cancer. *J Clin Oncol* 1993;11:1943–1951.
15. Seidman A, Norton L, Reichman B, et al. Preliminary experience with Paclitaxel (Taxol) plus recombinant granulocyte colony stimulating factor in the treatment of breast cancer. *Semin Oncol* 1993;20:40–50.
16. Renato AVO, Hoefnagel CA, van der Schoot JB. Nuclear medicine in the monitoring of organ function and the detection of injury related to cancer therapy. *Eur J Nucl Med* 1993;20:515–546.
17. Abdel-Dayem HM, Sanchez J, Al-Mohannadi S, Kempf J. Diffuse thallium-201-chloride uptake in hypermetabolic bone marrow following treatment with granulocyte stimulating factor. *J Nucl Med* 1992;33:2014–2016.