This apparently valid prescription would not meet the NRC's requirements. In the prescription displayed above, the physician relies upon the pharmacist to compound a drug that meets the requirements set forth in the prescription.

The radiation protection for the patient should be regulated in the licensure of the physician and the pharmacist to practice their respective professions. The regulations should be amended in order to allow the pharmacist to serve a professional role with respect to compounding radioactive drugs.

The nuclear pharmacist is the best trained health care provider to assume that role.

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Radioimmune Imaging of Bone Marrow in Patients

TO THE EDITOR: We have read with interest the paper of Duncker et al. (*1*), which caused us to raise some questions and to offer some comments.

Questions

1. With regard to the staging of patients as mentioned in Table 1, does it correspond to initial staging before surgery or to the staging at the time of the bone marrow imaging? Three patients (7, 10, and 16) would indeed have to be Stage IV because of metastasis in other organs (lung and bone, liver, peritoneum, respectively) and eight others on the basis of the bone scan results.

2. Would the authors clarify the notion of "extension" used in Table 1 as well? Do they mean—again— at the initial (clinical) staging before surgery, the anatomopathologic status of the surgically removed axillary nodes ("lympathic nodes") or the classification at the time of bone marrow imaging? The presence of involved lymphatic nodes or local extension would mean in the last case that these patients are relapsing ones?

3. What do the authors mean by "benign bone scan" (as stated for Patients 6, 10, and 23)? Do they mean abnormal bone scan presentations that might be interpreted as non-metastatic? If yes, we cannot agree with Duncker et al. because in breast cancer, as well as in all cancerous diseases, all bone scan abnormalities have to be controlled regardless of their diagnostic interpretation.

4. In their discussion, the authors say that they applied only local treatment in patients where a single metastatic lesion is seen on the bone scan. Do they mean local x-ray therapy? Their therapeutic attitude is somewhat surprising and their conclusion "modification of treatment" only reflects this situation.

5. Do the authors consider that marrow activity at the skull level is normal? In our experience, normal patients without cancerous diseases and without hematopathy (the term being largely understood) may normally present no marrow activity at either the skull level or at the level of the mid-third of the femur. We therefore consider that there is marrow extension if there is clear activity in the skull and in the mid-third of the femur or if we have clear activity up to the distal part of the femur.

Comments

1. Unfortunately, we cannot agree with the authors' comment: "... it seems possible that sometimes bone marrow is not affected by these (benign) diseases." Based on our experience, we can say that in some presentations of Paget's disease, fresh fractures and osseous hemangiomas (*2*), appear as cold defects on bone marrow scans and that the differential diagnosis of bone marrow defects remains to be established, since there is hyperactive foci on conventional bone scans. On the other hand, irradiated regions (*3,4*) also appeared as cold defects on marrow scans.

2. Patients with abnormal bone marrow expansion would have to be followed carefully, because they are at risk of relapse; nevertheless, they often remain disease-free for longer intervals than others without marrow expansion (*4*). One possible reason for this situation that was not addressed by the authors is an activated reticuloendothelial status due to micrometastatic disease either in the bone marrow or in other organs as suggested previously on the basis of our results (*4*).

3. The use of monoclonal antibodies for the imaging of the bone marrow is highly questionable mainly as a systematic attitude for screening of bone marrow metastasis. Not only because of the possible development of human antimouse antibodies (a major drawback from a medical point of view) but also for economic reasons. What will be the price of such an imaging agent and its definitive contribution with respect to what can currently be obtained with less expensive products, such as colloids (*2-8*)? The authors do not compare and discuss their results with regard to these facts. We agree that the accumulation of these agents in the liver represents a main drawback. In a review of 77 patients with bone metastasis, however, isolated lesions involving the last thoracic and first lumbar vertebras represented only 6.5% (*2*). We agree that marrow imaging with labeled leukocytes or monoclonal antibodies shows more lesions and gives more impressive pictures than colloidal scans, but their use would really modify the staging of the patients in as much as *only* 6.5% of those with skeletal metastasis. On the other hand, the realization of hepatic SPECT investigations with small-sized colloids (human serum albumin nanocolloids or Sb2S3 colloids) allows the detection of liver metastasis [in 19/53 patients with Stage IV breast carcinomas (*4*)] that cannot be obtained with antibodies. Finally, marrow imaging with antibodies will probably meet the same limitations as marrow scans using colloidal agents. Small (and sometimes large) metastases detected on bone scans that involve the skull, the ribs, and femurs may indeed be missed (*2-5*) regardless of the tracer used (*2,9*).

We agree with the authors that bone marrow imaging is useful in cases of dubious bone scan presentation as well as in cases of clinical suspicion of bone metastasis, as has been previously concluded by several authors (*3-7*). The use of antibodies in such circumstances should be limited in the future to situations where the use of colloidal agents are not

advantageous. In addition, ^{99m}Tc-HMPAO labeled leukocytes may give the same type of distribution activity in the marrow and thus may be used in these situations (*2,9*). Lastly, what about the possible consequences of repeated injections of such antibodies—one of the most interesting utilizations of marrow imaging is management and follow-up of patients under treatment (*5,6*).

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REPLY: We thank Drs. Bourgeois and Fruhling for their interest in our work. Regarding our staging of patients, as explained in the Methods section (*1*), Table 1 presents the stage of the patients when they were referred to our laboratory (before bone studies). Table 1 also presents the extension of the disease disclosed in addition to bone involvement, including extension revealed by the work-up performed simultaneously, bone studies. For example: Patient 10 was referred fo evaluation as Stage III. Axillary nodes were apparent at pa pation. The bone scan was interpreted as primarily benig (degenerative disease). Bone marrow imaging revealed tw cold foci, which turned out to be metastases at follow-up. CAT scan of the abdomen performed at the same time as th bone studies revealed liver metastases.

Bone scans in cancer patients can be interpreted as primar ily benign if only abnormalities more likely to correspond to benign disease are observed (i.e., aligned hot foci in the ribs, hot patella, increased uptake in the periarticular regions in patients with chronic arthritis) (*2*).

In breast cancer, a patient who presents with a single metastatic bone lesion may benefit from local treatment (radiation therapy) with or without endocrine therapy or chemotherapy (*3*). If this is the case, more agressive chemotherapy regimens are kept as second line treatment to be applied if there is progression of the disease or subsequent relapse. This therapeutic strategy has been shown to improve survival of these patients (*3*). Patients presenting with widespread bone metastases are prompted into agressive chemotherapy.

We did not use the presence of marrow activity in the skull as a criterion for bone marrow expansion. We used the classical criteria based on the presence of bone marrow in the distal femoral shafts (*4–5*).

Bourgeois and Fruhling seem to state in their letter that all benign bone diseases affect bone marrow and, therefore, produce cold defects in marrow scans. It seems possible to us that injuries to the bone starting from the cortical bone, i.e., degenerative arthrosis, may in their time course first involve the cortical bone, and later produce marrow injury (*6*). We have observed patients with peripheral increased uptake in adjacent vertebrae corresponding to degenerative disease in their bone scans who had normal marrow scans. In any case, further studies directed to assess bone marrow involvement in benign conditions have to be undertaken.

Bone marrow expansion may be multifactorial in origin (*4*). The cause of this frequent finding was out of the scope of our work. Silent micrometastatic disease may be one possible cause for marrow expansion even if hard to prove. We agree in that the possible development of antimouse antibodies may limit the use of this intact antibody for repeated injections (*1*). Marrow scans are not used to assess liver involvement in breast cancer; liver assessment is usually performed with CAT or ultrasonography.

We understand that Bourgeois et al. have had excellent results with colloidal agents in cancer patients. This has not been our experience. However, comparison between the antigranulocyte antibody and any other bone marrow imaging agent was not the aim of our study. We have shown that bone marrow scans performed with the antigranulocyte antibody detect more patients with metastatic bone disease than bone scans in primary breast cancer with suspected bone metastases. Furthermore, in patients with metastatic bone tissue invasion, bone marrow scans detect more metastatic sites than bone scans.

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