Malignant Pheochromocytoma Treated by I-131 MIBG

With few exceptions, the hope that radiopharmaceuticals could be developed to deliver local radiation to sites of cancer has not been realized. In some areas, we have achieved success—differentiated metastatic thyroid cancer can be ablated with I-131 (*1*,*2*) and P-32 has a therapeutic role in selected cases of polycythemia and thrombocythemia (*3*). Although many investigators are producing antibodies to cancer (both monoclonal and polyclonal) that can be labeled with radionuclides, to date the therapeutic effectiveness of radiolabeled antibodies has been disappointing. A significant proportion of the procedures in nuclear medicine are performed to establish the presence or absence of metastases. If the former, what then? It would be logical to use the diagnostic radiopharmaceutical therapeutically, either by using greater quantities or by switching the radionuclide to a β rather than γ emitter. From the diagnostic image one could determine the percentage uptake in the cancer and the effective half-time; if the mass of the cancer could be measured, dosimetry could then be calculated.

Over the years, Beierwaltes and his co-workers have pursued a goal of imaging the adrenal glands (*4*). They have shown the value of adrenal cortical imaging in diagnosing Cushing's and Conn's syndromes and have been able to differentiate bilateral and unilateral disorders (*5–8*). Next came the work with the adrenal medulla and pheochromocytomas. The remarkable progress in this area can be judged by the fact that in 1978 pheochromocytoma was detected as a "photopenic focus" on an iodocholesterol scintiphoto (*9*); however, in this issue of the *Journal*, Sisson et al. report patients with malignant pheochromocytoma who have been treated with I-131 meta-iodobenzylguanidine (MIBG), which is selectively concentrated in the adrenal medulla (*10*). This advance was the result of a sequence of logical steps.

Guanethidine and bretylium were known to be adrenergic-blocking drugs, and the combination of these compounds (benzylguanidines) produced even more active adrenergic blockers. Benzylguanidine is structurally similar to norepinephrine, which probably accounts for its uptake and storage in adrenergic vesicles. Iodine-125-tagged ortho-, meta- and para-benzylguanidines were synthesized and para-benzylguanidines (PIBG) and MIBG showed significant affinity for the adrenal medulla (*11*). Using I-131 PIBG, the adrenal medulla of dogs was imaged, the best images being obtained 3–5 days after i.v. injection of the radiopharmaceutical. Iodine-131 MIBG and I-125 MIBG were actively concentrated in the adrenal medulla of monkeys, and imaging was possible (*12*). The work was logically extended to study patients with diseases of the adrenal medulla. Normal adrenals are not seen on imaging, but Volk et al. (*13*) reported that hyperplasia of the adrenal medulla was visualized in patients with multiple endocrine neoplasia, and all eight cases of pheochromocytoma were correctly diagnosed, including metastases in two patients (*14*). These findings encouraged attempts to treat metastatic lesions with MIBG.

Malignant pheochromocytoma is a serious, albeit rare, condition. In most series of pheochromocytomas, approximately 10% are malignant, and they cause symptoms both by dissemination and by secretion of excess catecholamines. The latter can be counteracted in part by drugs including metyrosine, phenoxybenzamine, and propranolol. These drugs do not interfere with MIBG imaging or therapy. The metastatic lesions pose more of a problem, since they are generally unresponsive to standard antitumor chemotherapy and are not very amenable to external radiation therapy (*15*,*16*). Because of the ineffectiveness of standard therapies in this disease, the report of Sisson et al. is exciting, but it must be viewed with cautious optimism.

Two of the five patients improved subjectively, and had objective evidence of shrinkage of the cancer accompanied by a fall in biochemical abnormalities. In general, therapeutic doses were greater than 100 mCi and total doses ranged from 270–484 mCi. All of the patients tolerated the treatment well, and each patient received from 2–4 doses. Radiation doses to whole body were in the range 0.2–0.25 rad per mCi, and to the liver, spleen, and ovaries: 0.4, 1.6, and 1 rad per mCi,

respectively. From the published data it is not possible to calculate accurately the dose to the cancers in each patient, but in the two successful cases the dose is documented with reasonable certainty. These cancers received 15,680 and 19,790 rad. Lesser doses were ineffective, and it is reasonable to suggest that 15,000 rad and above should be the goal.

Were the investigators fortunate in the patient selection? The cancer in Patient 1 concentrated 55% of the first dose and 45%, 15%, and 12% of the subsequent three treatments. The cancers in the remainder of the patients accumulated from 0.8–2.5% of the total dose, and most of the published series describe uptake of approximately 1%. We recalled that uptake measurements are made on tumors deep within the body, surrounded by tissues that accumulate some of the radiopharmaceutical. The volume of the tumor was calculated from TCT studies assuming spherical configuration. Small errors in these measurements or in determining the effective half-time could make a substantial difference in radiation dosimetry. Precise measurement of each of these parameters is crucial for determination of the dose to be administered.

Very few investigators have experience with this radiopharmaceutical. The Ann Arbor group has demonstrated uptake in virtually every patient with pheochromocytoma. In one publication 23 of 24 were visualized, most of which were benign, and there were no false-positive studies (*17*). Hattner et al. (*18,19*) also had no false-positive studies, but they could visualize only eight of 12 proven tumors, and three of the false-negative results were in patients with malignant lesions.

Not every patient with malignant pheochromocytoma will benefit from treatment with I-131 MIBG. Some of the cancers (only time will tell what proportion) will not concentrate the radiopharmaceutical, and of those that do, some will not achieve sufficient concentration for adequate therapeutic effect. Fortunately, those patients with progressive disease most likely to need therapy appear to be the ones most likely to have significant uptake in their cancers. Care must be taken to suspend use of drugs such as reserpine and alphamethyldopa, which could interfere with uptake or incorporation of the radiopharmaceutical. One might question whether any pharmaceutical manipulation could augment uptake. The results of treatment of a larger number of patients and of patients from other centers are awaited with interest.

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Erratum

In the article entitled "Inverse Relationship Between Cardiac Accumulation of meta[^{131}I]-Iodobenzylguanidine)I-131 MIBG) and Circulating Catecholamines in Suspected Pheochromocytoma," Vol. 24, December 1983, pp. 1126–1134, the following corrections should be noted:

Page 1128, Figure 1. Legend should read: Change of heart intensity to patient with bilateral pheochromocytomas. A: Heart was not seen before surgery (Grade 0). B: Grade 2 heart intensity was observed after surgery. Region of heart indicated by closed arrow. Bilateral pheochromocytoma indicated by open arrows; L=liver, S=spleen, M=surface markers.

Page 1133, Figure 2. Legend should read: Grades of cardiac uptake. Posterior chest/abdomen images 24 hr after injection of MIBG. A=Grade 0, B=Grade 1, C=Grade 2, D=Grade 3. Region of heart indicated by arrow: L=liver, S=spleen, M=surface markers.