New Horizons for Therapeutic Nuclear Medicine in 1981

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The therapeutic approach of internally administered radiopharmaceuticals offers the potential to outmode the present approaches of conventional radiation therapy and chemotherapy because of three characteristics:

1. The therapeutic use of radiopharmaceuticals may deliver as much as orders of magnitude larger rad doses than conventional radiation therapy to target tissues, selectively irradiating these tissues internally in one radiation dose.

2. The therapeutic use of radiopharmaceuticals is followed by a lower incidence of leukemia and other cancers.

3. The treatment is comparatively noninvasive and nontraumatic.

We can now make this rather strong statement with fairly firm conviction because $Na^{131}I$ has been used since 1946 (33 years) to treat almost a million patients for hyperthyroidism (a) and in approximately 5000 patients for well-differentiated thyroid cancer (b); NaH_2PO_4 (P-32) has been used for 35 years to treat approximately 25,000 patients* with polycythemia vera (*3–5*).

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SELECTIVE TARGET IRRADIATION

Larger rad doses to target tissues can be delivered, with higher specificity for the target tissue, than by conventional radiation therapy. Saenger et al. (*3*) have recently reviewed the general background for this statement.

Graves' disease. In the treatment of Graves' disease with $Na^{131}I$, a thyroid gland that exhibits a 50% uptake at 24 hr averages 2,370 rads/mCi (*6*). It is generally agreed that an "ideal" dose to be delivered is 5,000–7,000 rads in the treatment of Graves' disease (*7*).

Well-differentiated thyroid cancer. Blahd has recently reviewed the radiation dose to target tissues in the treatment of well-differentiated thyroid carcinoma with $Na^{131}I$ (*2*). Effective tumor uptake is achieved if there is a concentration of 0.5% of the dose per gram of tumor tissue with a biologic half-life of 4 days. The administration of 150 mCi I-131 will deliver a tumor dose of approximately 25,000 rad, or five times the absorbed dose that can be achieved by a typical course of external radiation therapy. Moreover, this dose will be delivered to every functional metastasis in the body regardless of its size and location, and tumor tissue will receive several hundred times the irradiation received by the rest of the body.

Figure 1 is a graph of the radiation dose delivered in one of our patients to two thyroid remnants after attempted total thyroidectomy for papillary and follicular carcinoma of the thyroid. In our laboratory Koral et al. (unpublished data) with a treatment dose of 170 mCi of I-131 to this patient, delivered 30,800 rads to one remnant and 12,400 rads to the other, as measured by daily quantitative tomographic imaging (*8*).

Scott et al. (*9*) quantitated uptake of I-131 in metastases in vivo and determined that, for a 100-mCi dose, one patient received 69,000 rads in one lobe of the thyroid gland, and another patient received 26,000 rads to a metastasis in the temporal bone.

Hematoproliferative disorders. Silberstein has recently reviewed the radionuclide therapy of hematologic disorders (*4*). In the treatment of polycythemia vera and

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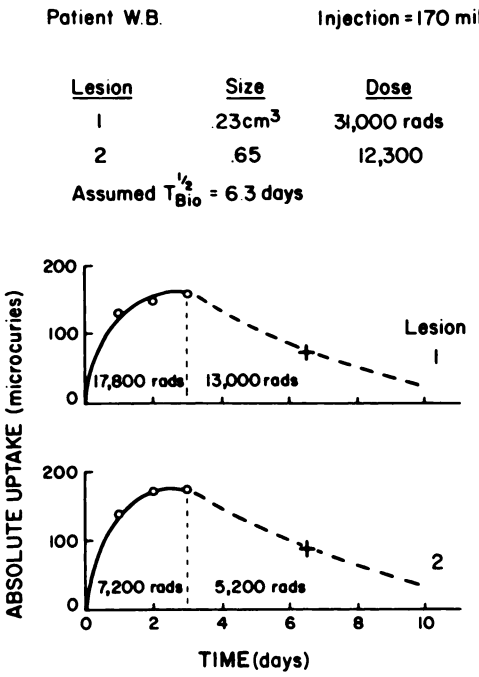

FIG. 1. Graph showing results of radiation dose to thyroid remnants after patient had surgery for total thyroidectomy.

leukemia, a range has been established for the dose from P-32 to bone marrow, liver, and spleen of from 20–50 rad/mCi injected. With few exceptions, P-32 has been used primarily to suppress hyperproliferative or neoplastic marrow cell lines, with the goal of control rather than cure. Thus, marrow doses of approximately 80–200 rads have been utilized. This is within the range of the estimated D_0 for human marrow, i.e., the radiation dose that will irreversibly inhibit cell division in 63% of cells so treated (*10*).

LOW RISK OF CARCINOGENESIS

The therapeutic use of radiopharmaceuticals is followed by the lowest incidence of leukemia and other cancers.

Treatment of hyperthyroidism with $Na^{131}I$. Becker has recently made the summary statement in this *Journal* (*1*) that ". . . after 30 years of use in almost a million hyperthyroid patients, I-131 is today considered to be the most effective and efficient therapy available for the definitive management of hyperthyroidism in adults. There is reason for confidence in its safety, since studies of large numbers of patients with long and almost complete follow-up have not shown any increase in leukemia or thyroid cancer, and no obvious birth defects or genetic changes have appeared in the offspring of patients treated with I-131" (*11,12*).

These same statements can be made for fewer numbers of patients concerning the treatment of Graves' disease in children (*13,14*) and—with orders of magnitude larger doses—concerning in the treatment of thyroid cancer in children (*15*).

Leukemia following treatment of thyroid cancer with $Na^{131}I$. Of 532 patients treated with I-131 since 1947, we have had one patient with known chronic lymphatic leukemia at the time the first treatment dose was administered. In 1977, a man whose occult thyroid carcinoma (due to irradiation to the head, neck, or upper chest as a child) was discovered during surgery for a parathyroid adenoma causing hyperparathyroidism developed granulocytic leukemia 1 yr after a 100-mCi treatment dose of I-131. We have had no other patients with leukemia in follow-ups during 32 yr, including two patients given a total dose of more than 1 Ci. In view of our 33-yr experience, it is important to note that all cases of leukemia following I-131 therapy have been detected within 5 yr after the first treatment with I-131 (*16,17*). Pochin has experienced a 2% incidence of leukemia in his treated patients (*17*). He gave repeated doses of 150 mCi, however, at 7- or 8-wk intervals.

We believe that the bone marrow should be given a year to recover between doses (*18*) whenever possible. This observation, made in 1963, has now been upheld by Rubin et al. (*19*) and Knospe et al. (*20*). Rubin's group, utilizing Tc-99m SC bone-marrow scanning, indicates that prolonged suppression of bone marrow occurs immediately following completion of segmented sequential irradiation in patients with Hodgkin's disease and persists for 1 or 2 yr. They present new evidence that, if doses in the 4000-rad range are fractionated, partial to complete bone-marrow regeneration occurs at 2 yr in 85% of the exposed bone-marrow sites. Knospe et al. (*20*) studied extensively irradiated patients with Fe-52 bone-marrow scanning from 0–73 mo after irradiation. Marrow regeneration was observed in most patients after intervals of 12 mo or longer. Blood-count cytopenias were almost always restricted to the first year after irradiation.

Other malignancies. We have not analyzed the incidence of other malignancies in our 532 patients treated with I-131 for thyroid cancer, but we have looked for tumors in other organs exposed to increased concentrations of I-131: choroid plexus, salivary glands, stomach, kidneys, and bladder. The two patients with parotid-gland tumors developed them before the original diagnosis of thyroid cancer. Massaferri et al. (*21*) noted a 3.5% incidence of at least one other malignancy. Three individuals had two other malignancies. In over half the cases (11 individuals) the other malignancy clinically preceded the thyroid cancer.

An increased frequency of malignant tumors of other organs is reported to occur in patients with thyroid cancer (*22,23*). Breast cancer is the most common such neoplasm, but a number of other neoplasms, including many in the head and neck structures, have been observed (*21*). Wyse (*23*) found that after a diagnosis of thyroid cancer has been established, a patient suffers an increased risk that a second primary neoplasm may de-

velop, with an attack rate of 1.4% per year.

Anaplastic transformation. The conversion of a well-differentiated thyroid carcinoma to anaplastic cancer has been noted in a small but important number of patients. Because in many of the reported cases, the original tumor had been irradiated, some speculate about the possibility of a causal relationship between radiotherapy and subsequent anaplastic transition of the tumor. Mazzaferri et al., however, observed that only about half of the reported patients in which differentiated tumors ultimately gave rise to anaplastic cancers had a documented history of previous irradiation (*21*).

Chemotherapy and conventional radiation therapy. The "normal" incidence of leukemia and second tumors after I-131 therapy is in sharp contrast to the hazards of chemotherapy, especially combined with conventional radiation therapy. Chabner, from the National Cancer Institute, in an editorial (*24*) reviewed the observations that in ovarian cancer patients living 2 yr after initiation of chemotherapy, the risk of developing acute leukemia is increased by a factor of 67–171. Similarly in patients with Hodgkin's disease the risk of developing a second cancer 4 yr after nodal irradiation and chemotherapy is increased by a factor of 21!

These data at 2 and 4 yr after apparent freedom from disease after conventional radiation therapy and chemotherapy are in striking contrast to our data at 33 yr in patients freed of lung metastases from well-differentiated thyroid cancer by all criteria (chest radiograph and I-131 lung scans) for as long as 27 yr after treatment (*25,26*, Beierwaltes, WH, unpublished data).

New data on 103 patients with metastases from well-differentiated thyroid carcinoma *outside the neck* show that I-131 treatment doubles or triples the survival time in those patients freed of their distant metastases by this treatment.

Cady et al. (*26*) have also produced new encouraging data on 600 patients with well-differentiated thyroid carcinoma, diagnosed between 1931–1960, with a 98% followup for 15–45 yr. He found that the recurrence rate and death rate were significantly different in defined high-risk and low-risk groups. Men <41 years of age and women <51 years of age were placed in the low-risk group, and older patients in the high-risk group. The recurrence rate after surgery was 33% in the high-risk group and 11% in the low. The death rate was 27% in the high-risk group and 4% in the low. The I-131 cure rate in patients with *metastatic disease* was 70% in the low-risk group and 10% in the high.

Thus after following patients for up to 33 yr after I-131 treatment of thyroid cancer, we see them freed of their metastases by all criteria, and without the well-documented increased risk of leukemia and other tumors observed in the treatment of other cancers with conventional radiation therapy and chemotherapy.

As an aside, however, it should be remembered that in the National Cooperative Thyrotoxicosis Study, one of the most interesting observations was that Graves' disease itself was associated with an incidence of leukemia 50% more common than in the general population, whether the hyperthyroidism is treated surgically or with I-131 (*11*). This same observation had been made earlier by Ultman et al. concerning lymphomas (*27*), and in some cases of the Cooperative Thyrotoxicosis Study it appeared that the lymphoma had preceded the I-131 therapy (Saenger, EL, personal communication).

P-32 in myeloproliferative disorders: Polycythemia vera. Over a period of 40 yr (*28*), the unequivocal efficacy of P-32 in the treatment of polycythemia vera has been well documented (*4*). It prolongs median survival to 13–16 yr from onset, but in retrospective studies the role of P-32 in leukemogenesis in polycythemia has been suggested as well as the possibility of its increasing the risk of transition from polycythemia vera to myeloid metaplasia (*4*).

The Polycythemia Study Group (PVSG) has been comparing the results, in a large group of patients, of therapy with P-32 with the results of chlorambucil treatment (both using phlebotomy as needed) and with phlebotomy alone (*4*). This study group has reported recently that their treatment of choice for polycythemia vera is now P-32 plus phlebotomy as needed to maintain normal hematocrit and platelet counts. They are no longer treating patients in their study with chlorambucil (an alkylating agent) because of the significantly increased incidence of acute leukemia in that group. After follow-up of 4–10 yr, their latest available results showed that acute leukemia developed in one of 134 patients treated with phlebotomy alone, six of 156 on P-32, and 15 of 141 on chlorambucil. Overall survival was about equal with the P-32 plus phlebotomy and with phlebotomy alone, although the latter causes a higher incidence of thrombotic events.

As a result of these findings, oncologists at the University of Michigan were sufficiently impressed by the higher rate of leukemia in the chlorambucil-treated group to request the Division of Nuclear Medicine in June of 1980 to resume the P-32 treatment of polycythemia vera as the routine treatment of choice.

INVASIVENESS AND INJURY

The radiopharmaceutical treatment is less invasive and traumatic than conventional radiation therapy and cancer chemotherapy.

On April 5, 1978, at the 69th Annual Meeting of the American Association for Cancer Research in Washington, DC, Zubrod said in his Presidential address that "combination chemotherapy has a number of serious drawbacks: complexity, long duration of treatment, expense, toxicity, and perhaps worst of all a growing problem of induction of leukemia and other second tumors" (*29*).

The treatment of well-differentiated thyroid cancer after surgery by having patients drink a few milliters of water through a paper straw, with no more than minor complications (*2*), is in striking contrast to the long duration and toxicity of chemotherapy and the weeks of daily radiation treatments.

Likewise in the P-32 treatment of polycythemia vera, the P-32 can occasionally be given in a single oral or intravenous dose. Radiation sickness (including gastrointestinal symptoms) has not been described with the P-32 doses used to treat hematologic disease (*4*).

Future progress with radiopharmaceutical therapy? Because the radiopharmaceuticals can deliver to the target tissue, selectively and noninvasively, radiation doses sometimes orders of magnitude higher than can conventional radiation therapy, and can compete favorably with chemotherapy, all without the rising high incidence of leukemia and second tumors, they have the potential to outmode conventional modern radiation therapy and chemotherapy if we in nuclear medicine can develop new radiolabeled compounds for the treatment of other cancers using our present 33- to 40-yr experience with the treatment of well-differentiated thyroid cancer. What are our prospects of developing these new radiotherapeutic compounds to expand the nuclear medicine approach to therapy? Our laboratory has been working on this approach ever since December 7, 1951, when we started our first treatment, eventually successful, of a metastatic malignant melanoma with I-131-labeled immunoglobulins derived from rabbits immunized to a crude saline extract of the patient's own malignant cells. Our current probable success is with a new radioiodinated adrenal medulla imaging agent developed in our laboratories (*30,31*, Beierwaltes, unpublished data).

I-131-labeled meta-iodobenzylguanidine and the adrenal medulla. After a 13-yr effort to develop a radioiodine-labeled analog of dopamine for the diagnosis and therapy of adrenal medullary tissues, our radiopharmaceutical group at the University of Michigan is evaluating the new agent meta-[^{131}I]iodobenzylguanidine (*30,31*, Beierwaltes, WH, unpublished data) for the treatment of adrenal medullary hyperplasia to prevent (a) the 25–32% death rate of pheochromocytoma in the MEN IIa syndrome (*32*), or (b) the risk of Addisonian crises from bilateral total adrenalectomy. Present calculations in a patient with metastases from adrenal medullary carcinoma to the brain, skull, axial skeleton, and abdomen show that we will be able to deliver 5000 rads/100 mCi of I-131 MIBG in a fashion similar to the treatment of well-differentiated thyroid carcinoma with Na^{131}I. We administered a 100 mCi treatment dose, February 15, 1981, hoping to parallel the results of 532 well-differentiated thyroid carcinomas treated with Na^{131}I.

Radiolabeled inhibitors for enzymes present in a rich concentration in cancers. We first achieved diagnostic imaging of the adrenal cortex in the dog with I-123-labeled SKF 12,185, a reversible enzyme inhibitor of 11 β hydroxylase (*33*). Diagnostic trials in human carcinoid have begun with para-iodophenylalanine, an irreversible inhibitor of tryptophan hydroxylase, a rate-limiting enzyme that converts tryptophan to serotonin in carcinoid. Para-iodophenylalanine showed a higher diagnostic uptake in the mouse mastocytoma model of carcinoid than did 5-iodo- and 6-iodo-tryptophan and para-iodoamphetamine (Mangner, T, unpublished data). We have demonstrated that ornithine decarboxylase activity is increased in most cancers (*34*) by a factor of 150–300, as compared with the tissue of origin, but histaminase is increased strikingly only in medullary thyroid cancer and small-celled cancer of the lung (*35,36*).

Radioiodinated antibodies and Fab fragments. Pressman and Keighley first labeled antibodies with radioactive isotopes in 1949 (*37*). We are credited with the first treatment of a human cancer with radioiodinated antibodies (*38–40*). In the I-131-antibody treatment of a malignant melanoma, referred to earlier, the patient was given the radioimmunoglobulin in a continuous intravenous drip, and was free of his disease by all criteria in May, 1952 (*40*). After failure to repeat this success in 11 consecutive patients, I concluded that a cancer-specific antigen was necessary. In 1971, Quinones, Mizejewski, and I published the first photoscan detection of a human carcinoma (choriocarcinoma) growing in a hamster's cheek pouch, using radioiodinated polyclonal immune IgG to human chorionic gonadotropic hormone (hCG) (*41*). Three years later, Goldenberg et al. (*42*) and Hoffer (*43*) published the use of this model for photoscan detection of carcinoma of the colon using radioiodinated immune IgG to CEA antigen. Goldenberg and DeLand (*44*) then used affinity-purified polyclonal antibodies to achieve diagnostic detection of a wide variety of human neoplasms. They originated the descriptive term "radioimmunodetection."

Since then there has been a veritable explosion in the use of radioiodinated antibodies to achieve diagnostic location of cancer. An entire issue of *Cancer Research* was devoted to the publications of a wide variety of presentations on this subject in a symposium held by Goldenberg and DeLand in Lexington, Kentucky, July 19–21, 1979. Order et al. reviewed their promising early results in therapy of neoplasms with I-131-labeled anti-CEA polyclonal immune IgG in that issue (*45*).

Our polyclonal IgG antibody to HCG was 99% immune-nonspecific, but this antibody, purified, has been used successfully for diagnostic location of lung cancer in man (*46*).

We are thoroughly excited by this finding because *monoclonal* antibodies are 99% immune-specific and we have started diagnostic and therapeutic trials with a radioiodinated monoclonal antibody to the beta subunit

of hCG (Khazaeli, M, unpublished data). We find that most cancers have hCG on the cell surface and in the cytoplasm (*47*,*48*).

Radioiodine-labeled monoclonal antibodies have already successfully located tumors in animals (*49*).

Obviously, there will be great competition among a large number of investigators, with the benefit to the patient, to develop the most effective diagnostic and therapeutic radioiodinated monoclonal antibody (and Fab fragment) for a wide variety of cancers.

In summary, we have attempted to document our opening statement that the radionuclide approach to the treatment of cancer has the potential to outmode most modern radiation therapy and cancer chemotherapy. 1981 promises to be an exciting year for the prospects of radionuclide therapy.

FOOTNOTE

* Wasserman LR, personal communication, 1/6/81: There is an occurrence of about 1,000 new cases of polycythemia vera each year. For about 20 years, phlebotomy and $Na^{32}P$ were used to treat all cases, or about 20,000 patients. During the past 15 years, P-32 has been used to treat about one third of these patients, or about 4,985, for a total of ~25,000 patients.

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