

Systemic Targeted Radionuclide Therapy—Positioned for a Take-off

a report by

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Shortly after the observation in the late 1800s that radioactive emissions could be used to treat cancer, it became apparent that increasing the dose of radiation delivered to tumors resulted in greater local control and a potential cure, but that the ultimate limiting factor in dose delivery was the frequently low tolerance of normal tissues. Unlike the tissue reactions produced secondary to many other medical interventions, radiation damage to normal tissue was often irreversible and onset was frequently noted long after the radiation had been administered. Early techniques in brachytherapy (radioactive implants directly into tumors) reduced doses to normal tissues somewhat, but employed isotopes of such high energy (e.g. radium and cesium) that normal tissue damage was still inevitable in many cases, and normal tissue tolerance remained a limiting factor in radiation applicability for almost a century. The Holy Grail in the use of radiation for cancer therapy became the elusive agent(s) that could selectively target tumor tissue and spare normal tissue. Progress in external beam radiation therapy (EBRT) equipment and techniques, first with high-energy beams from linear accelerators, then three-dimensional (3-D) conformal radiation, intensity-modulated radiation therapy (IMRT), and, more recently, proton beam radiation produced dramatically reduced doses to normal 'transit' tissues, but limitations persisted.

In the 1940s, the availability of iodine-131 (^{131}I) in the sodium iodide form ushered in a new era and potential for radiation management of cancer and certain benign disorders of the thyroid gland. The nature of selective physiologic/metabolic localization of iodine in the thyroid gland, with rapid excretion of residual iodine, was the prototype for subsequent investigation and utilization of systemic radionuclides. Iodine fulfilled most of the characteristics of the ideal systemic targeted radionuclide therapy (STaRT) agent in that it localized selectively in the

target tissue, had a favorable physical profile (physical and biological half life and decay scheme), had a gamma component that permitted imaging for dosimetry and documentation of localization, was reliably and readily available, and was inexpensive.

The fact that no carrier molecule or carrier-binding agent was necessary only added to the isotope's potential and effectiveness. Unfortunately, the use of the unbound isotope was limited to the relatively uncommon well-differentiated thyroid cancers that demonstrated iodine affinity, such as the follicular and papillary variants.^{1,2}

In the 1960s through the 1980s, interest peaked in the use of phosphorus-32 (^{32}P) in both aqueous and colloidal formulations. Intravenous aqueous ^{32}P (as Na_2PO_3) proved to be effective in the systemic management of polycythemia vera and chronic myelogenous leukemia, as well as for palliative treatment of metastatic disease in bone.

Use in the hematological malignancies was soon eclipsed by the introduction of more effective chemotherapeutic compounds, and other radioactive agents proved to be more efficacious and more easily administered for management of bone metastases.

The intra-cavitary use of ^{32}P for control of malignant pleural effusions and ascites was highly effective, and the agent was employed routinely in this regard. In the 1980s, there was also considerable interest and investigation related to the use of the agent for subclinical mesothelial disease from ovarian malignancies when used in conjunction with debulking surgery or as adjuvant management. Studies carried out by the Gynecologic Oncology Group and individual centers proved efficacy, but in the presence of inhomogeneous abdominal distribution of isotope, as was often the case post-

1. Coover L R, et al., "Therapeutic I-131 in outpatients: a simplified method conforming to the Code of Federal regulations, title 10, part 35.75", *J Nucl Med* (2000);41: pp. 1,868–1,875.
2. Barbaro D, et al., "Radioiodine treatment with 30 mCi after recombinant effectiveness for postsurgical remnants ablation", *J Endocrinol Metab* (2003);88: pp. 4,110–4,115.

operatively, complications proved to be unacceptable. ^{32}P use waned in the late 1980s, until Order and others suggested the potential for direct tumor instillation of the agent in association with materials to produce arteriolar/capillary blockade and, therefore, promote isotope retention. High tumor doses were demonstrated with anecdotal evidence of efficacy.

More recently, the agent has been used for management of recurrent joint effusions in hemophiliacs and patients with rheumatoid arthritis (radiosynovectomy).³⁻¹⁰

In the 1990s, strontium-89 (^{89}Sr) chloride (Metastron®) and samarium-153 (^{153}Sm) ethylene diamine tetramethylene phosphonate (EDTMP) leixidronam (Quadramet®) were introduced for palliative treatment of painful osseous metastases. The agents are administered via an intravenous approach and localize in bone because of their similarity to calcium analogs. They demonstrate rapid clearance through the urinary tract of any isotope not deposited in bone and have preferential localization in sites of active osteogenesis. ^{89}Sr is a pure beta emitter and is not suited for imaging. ^{153}Sm decays with beta and gamma emissions, which does allow for image-based dosimetry and documentation of localization. Because targeting is based on their chemical resemblance to calcium and local metabolic activity in osteoblastic bone lesions, the agents do not require carrier compounds.¹¹⁻¹⁶

The use of all of the products described thus far permitted radiation oncologists and nuclear medicine physicians to gain expertise and familiarity in handling the systemic agents, but the limitations inherent in chemical/metabolic targeting or direct focal deposition of isotope were significant and use was limited to a small cohort of patients. In 1975, Jerne theorized, and Kohler and Milstein ultimately described, hybridoma techniques for production of monoclonal antibodies in quantities sufficient for clinical investigation and use. This discovery opened new horizons in consideration of STaRT techniques and ultimately earned them the Nobel Prize in Medicine in 1984. The work of Order and colleagues at Johns Hopkins University, and that of other centers around the world utilizing monoclonal and polyclonal antibodies, raised additional interest in STaRT and enthusiasm suggested that the Holy Grail of radiation oncology, deposition of radioactivity within the cancer cell while sparing normal tissue, was around the corner. Initial clinical trials made use of polyclonal antibodies derived from multiple animal species, targeted to antigens such as ferritin and carcinoembryonic antigen (CEA).

Ferritin had been found to be over-expressed in Hodgkin's disease, a number of non-Hodgkin's lymphomas, and Kaposi's sarcoma. CEA was over-expressed in a variety of glandular cancers, especially those arising in the gastro-intestinal tract. The isotope most frequently used for therapeutic labeling was ^{131}I

3. Potter M E, et al., "Intraperitoneal chromic phosphate in ovarian cancer: risks and benefits", *Gynecol Oncol* (1989);32: pp. 314-318.
4. Soper J T, et al., "Adjuvant therapy with intraperitoneal chromic phosphate (^{32}P) in women with early ovarian carcinoma after comprehensive surgical staging", *Obstet Gynecol* (1992);79: pp. 993-997.
5. Spanos W J, et al., "Use of P-32 in stage III epithelial carcinoma of the ovary", *Gynecol Oncol* (1994);54(1): pp. 35-39.
6. Spencer T R, et al., "Intraperitoneal P-32 after negative second-look laparotomy in ovarian carcinoma" *Cancer* (1989); 63(12): pp. 2,434-2,437.
7. Order S E, et al., "A new method of delivering radioactive cytotoxic agents in solid cancers", *Int Jour Rad Oncol Biol Phys* (1994);30: pp. 715-720.
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because of its availability, low cost, stable binding properties, relative ease of binding to the carrier molecules, and inherent physical properties. Unfortunately, significant difficulties with the agents outweighed advantages. Radiation safety concerns remained problematic, patients with reduced bone marrow reserve were often placed at significant risk because of high bone marrow doses, labeling was inefficient and targeting not highly selective or specific. The use of polyclonal antibodies from a number of species rather than murine monoclonal antibodies reduced immunogenicity somewhat, but allergic reactions to the agents remained evident. Perhaps the paramount clinical disadvantage was the lack of ability to integrate the agents into a coherent multimodality program of cancer care after studies investigating them as monotherapy in advanced disease proved disappointing. Thomas and colleagues capitalized on the marrow-ablative properties of several of the compounds by integrating them into bone marrow transplant procedures as induction therapy in leukemia and lymphomas (for which Thomas was ultimately awarded the Nobel Prize in 1990).

As with many other advances in medicine, the ability to exploit the real potential of STaRT awaited a confluence of scientific discoveries in a variety of disciplines:

- radiochemistry development enabled creation of more stable carrier: isotope bonds that could resist breakage in circulation or in passage across cell membranes;
- developments in polymer chain reaction techniques enabled access to large quantities of candidate carrier agents;
- completion of the Human Genome Project expedited identification of numerous potential cell surface and intra-cellular targets;
- the ability to utilize antibody fragments and to employ humanized or human antibodies significantly reduced the problems of immunogenicity; and
- resurgence of interest in molecular biology, molecular chemistry and genetics introduced a new generation of scientists to the potentials of STaRT.

In 2003, the US Food and Drug Administration (FDA) approved two radioactive labeled monoclonal

antibodies for the treatment of follicular non-Hodgkin's lymphoma that had failed other therapies. Both agents employ monoclonal antibodies that are targeted to the CD20 antigen present on the surface of certain normal and malignant B-cell lymphocytes.¹⁷ Ibritumomab tiuxetan (Zevalin[®]), an immunoglobulin G (IgG)-κ monoclonal antibody, employs yttrium-90 (⁹⁰Y) as its therapeutic label. ⁹⁰Y decays by pure beta emission, presenting minimal radiation safety or handling problems, and is well suited for outpatient administration. A T1/2 of 64.1 hours permits flexibility in scheduling and administration.

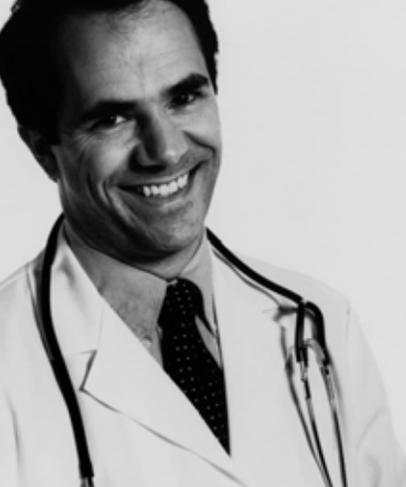
The effective path length of the 2.3 maximum particle energy (MeV) allows for 'cross-firing' of radiation requiring only relative proximity to the cancer cell. Because beta emissions do not permit adequate dosimetric visualization, documentation of localization and dosimetry is performed prior to the therapeutic administration using an indium-111 diagnostic label.

Tositumomab and ¹³¹I tositumomab (Bexxar[®]) employs a murine IgG_{2a} monoclonal antibody also directed against the CD20 antigen. A tracer dose of the agent is administered to document localization and carry out dosimetry, followed seven to 14 days later by the therapeutic administration.

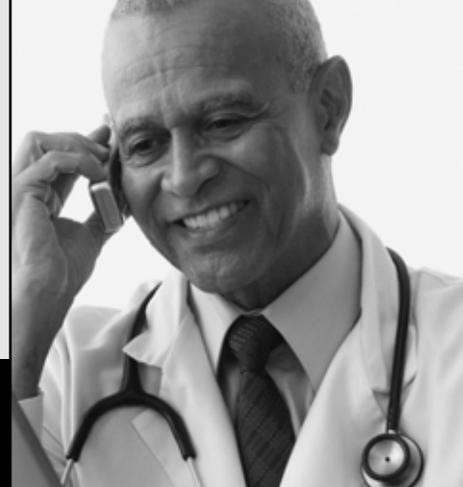
Both agents have significant potential to induce prolonged and severe cytopenia, as would be anticipated in a population of patients that has already been exposed to multiple courses of chemotherapy and has an intrinsic primary hematological disease. Despite this adverse reaction, responses have been such that the agents are being introduced earlier in the natural history of the diseases for which they are currently indicated, and new indications are under investigation.

Ibritumomab tiuxetan and tositumomab have clearly established the long-sought proof of principle that direct targeting of tumor cells with radiolabeled compounds can evoke profound anti-tumor effect. Problems that remain to be solved include improved targeting of more common solid tumors, attainment of higher tumor-to-background ratios, adoption of candidate radioisotopes with more favorable physical properties than those currently in use, and a more scientifically sound incorporation of the techniques into multimodality cancer care. Advances in tumor biology, radiochemistry, and nanotechnology delivery systems almost guarantee that this progress will come at an explosive pace. ■

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