Development of Miniature High-Dose-Rate ^{252}Cf Sources for Boron-Enhanced and Fast Neutron Brachytherapy

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Summary

Californium-252 neutron brachytherapy (NBT) is extremely effective in causing rapid regression of bulky, localized, radioresistant (hypoxic) tumors. However, availability of a miniature, high-dose-rate (HDR) ^{252}Cf source would greatly improve the clinical methodology. Oak Ridge National Laboratory (ORNL) and Isotron, Inc., have co-developed a new generation of these ^{252}Cf sources suitable for interstitial and intracavitary HDR NBT, with capsule dimensions comparable to those of HDR photon brachytherapy sources. Isotron's NBT system, which includes a remote afterloader system (RAS) for source delivery, will treat adult and pediatric cancer in eighteen sites throughout the body. The future integration of Isotron's NBT system into a multi-modality therapy with boronated pharmaceuticals is particularly exciting.

Introduction

The effectiveness of ^{252}Cf brachytherapy (i.e., insertion of a small radioactive source through a catheter into the tumor) has been demonstrated for 30 years in over 6000 patients. NBT is advantageous in limiting dose to healthy tissue by placing the ^{252}Cf source directly into the tumor, with maximum dose to the cancerous cells and attenuated dose to more distant, healthy tissue. NBT has the advantage over conventional photon and gamma brachytherapy for greater effectiveness in treating radioresistant tumors such as bulky and late-stage tumors, melanomas, and glioblastomas. A recent study[1] demonstrated a 14% improvement in 5-year survival statistics of cervical carcinoma when ^{252}Cf brachytherapy was included in a gamma irradiation regimen, and even greater improvement for late stage tumors. Cancer treatments using NBT are increasing rapidly, most notably in China.

Iridium-192 photon brachytherapy is the current standard for clinical HDR brachytherapy. Small (~1-mm outer diameter) HDR ^{192}Ir sources can provide treatments in as few as 5 to 10 minutes. In contrast, ^{252}Cf

interstitial (internal organ) brachytherapy has been limited to low-dose-rate treatments with lengthy treatment times[2] because of the difficulty in miniaturizing high-activity ^{252}Cf source forms. HDR ^{252}Cf sources with an outer diameter of ~3 mm have been fabricated in Russia. Such sources are appropriate for intracavitary brachytherapy (e.g., gynecological, rectal, head, neck, and oral cavity treatments), but are not appropriate for interstitial brachytherapy such as brain tumors.

Californium-252 NBT has not achieved widespread use because of the preference by radiation oncologists for miniature HDR sources coupled to a RAS for source delivery. HDR treatments use 500 μg or more ^{252}Cf (total fast neutron emission $>10^9$ s^{-1} at 2.1 MeV average energy).[2] Successful fabrication of such sources will provide interstitial ^{252}Cf treatments in reasonable times, permitting optimized treatments of tumors of the brain, breast, colon and rectum, esophagus, eye, lung and bronchus, prostate, gynecological tumors and melanomas, among others.

Materials and Methods

The U.S. Californium Program originally produced ^{252}Cf medical sources at Savannah River Laboratory. After the Californium Program was transferred to ORNL in the late 1980s, no further progress was made until 1995, when an ORNL "seed money" project explored the fabrication of thinner, higher-intensity ^{252}Cf source forms based on a cermet wire containing Cf_2O_3 interspersed within a palladium metallic matrix.[3] The smallest cermet wire fabricated within the hot cells was ~1 mm diameter.

In 1999, ORNL and Isotron, Inc., entered into a Cooperative Research and Development Agreement (CRADA) to further reduce the wire diameter and design a new family of medical sources. A series of engineering and fabrication tasks are required to develop a new miniature source design. The source capsule is designed specific to the source form. A means of attaching the capsule to a positioning cable (for remote afterloading) must be developed and tested. Welding of small capsules must be demonstrated. Process tooling must be designed and fabricated, and handling techniques developed. Special form testing is required to demonstrate a leak-tight source design. Fabrication procedures must be written and QA testing and documentation completed.

Results and Discussion

Major progress has been achieved to date. The ^{252}Cf-containing cermet wire was reduced to diameters smaller than any previously available. A suitable capsule-to-cable attachment has been demonstrated.

A commercial welding system has been demonstrated for miniature capsules, and modified for hot cell installation and use. Tooling for handling miniature source components has been designed and fabricated. Isotron's NBT systems combine the miniature high-activity neutron sources with a remote, automated storage and delivery system that will utilize the latest imaging, surgical, and patient treatment planning techniques available.

The first prototype sources have been designed for use with existing gamma-source applicators, achieving the desired miniaturization goal. Using a comparative figure of merit of encapsulated ^{252}Cf mass per total source volume, the first prototype sources are an order of magnitude better than existing interstitial sources. These are the first ^{252}Cf medical sources capable of providing HDR interstitial brachytherapy.

After initial clinical trials, coupling with boronated pharmaceuticals will be tested. Boron introduction into the treatment site via a direct intratumoral drug delivery technique will enhance dose within the tumor volume with corresponding reduction of dose to more distant healthy tissue. Dose to metastases will be enhanced due to preferential boron uptake by tumor cells, enabling better long-term tumor control.

Accelerator-based fast neutron therapy is the most common neutron-based method of cancer treatment, with approximately 1000 to 2000 patients treated annually around the world. NBT follows, with a few hundred patients a year (primarily in China and the Czech Republic), but is expected to increase rapidly with newly-established centers in China. Reactor-based neutron capture therapy treats a smaller number of patients.

China, the Czech Republic, and other centers in Eastern Europe use Russian-built sources fabricated at the Research Institute of Atomic Reactors (RIAR) in Dimitrovgrad. RIAR manufactures medical sources with neutron intensities ranging from 10^6 s^{-1} to 5×10^9 s^{-1} (>2 mg of ^{252}Cf). Specialists from RIAR in cooperation with physicians from Russia and other countries are developing neutron sources for a new generation of ^{252}Cf brachytherapy systems, such as the neutron knives (see below). RIAR and ORNL are the only producers of ^{252}Cf medical sources.

The 4th International Workshop on ^{252}Cf Brachytherapy was held in Bologna, Italy in June 2002 as part of the 5th International Topical Meeting on Industrial Radiation and Radioisotope Measurement Applications. The rapid expansion of NBT was highlighted by the Linden Neutron Knife Company, which installed the first NBT treatment unit in China in 1999, and now has 10 treatment centers in operation (>350 patients treated to date) and up to 30 centers planned. The Masaryk Memorial Cancer Institute in Brno, Czech Republic routinely treats ~80 patients annually. The workshop attendees agreed to establish the

International Californium-252 Brachytherapy Society (ICBS), with the following goals:

1. Share patient statistics and treatment information,
2. Standardization of treatments (develop ICRM-like standards), and
3. Provide a forum for members to meet and discuss issues of common interest. The attendees agreed to hold the next International Workshop on ^{252}Cf Brachytherapy in September, 2004, in China.

For standarization between treatment centers, the ICBS will evaluate issues such as the reporting of gray vs. gray-equivalent dose, the RBE values used by the centers for various tumors, and methods of neutron dosimetry. The previous experience of the neutron capture therapy community will provide a valuable starting point for ICBS evaluations.

Conclusions

New miniature ^{252}Cf sources designed for HDR interstitial and intracavitary brachytherapy will provide unprecedented treatments of glioblastomas and a variety of other radioresistant tumors. Significant progress had been made in demonstrating fabrication of prototype sources. Boron-enhanced NBT will be evaluated for tailoring dose to the tumor and reducing necrosis of healthy tissue. Continuing expansion of international treatments and collaboration is expected.

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