Development of Miniature Californium-252 Neutron Sources for Cancer Therapy

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INTRODUCTION

Californium-252 radioisotopic neutron source capsules have been used for brachytherapy treatment of radioresistant tumors for nearly 30 years. Brachytherapy, by temporarily placing one or more radioactive sources directly into the tumor via closed-ended catheters or needles, is much more effective in treating a concentrated, localized tumor than external beam therapy. The radiation is attenuated away from the brachytherapy source, maximizing the dose to the tumor while minimizing the dose to surrounding healthy tissues.

Treatments in the United States have relied on a manually afterloaded, low-dose-rate source design containing up to 30 μg of ^{252}Cf in a 2.8-mm-diameter by 23-mm-long capsule. Medium-dose-rate treatments (i.e., 100 to 400 μg of ^{252}Cf) require multiple sources, with potentially significant radiological exposure to the therapist handling the sources. Lengthy treatment times (typically ranging from 4 to 60 hours) can be avoided by the use of high-dose-rate (HDR) brachytherapy ($\geq$500 μg of ^{252}Cf), but this requires a remote afterloading system (RAS) with the source attached to a positioning cable. A 3-mm-diameter HDR source is used in Russian and Chinese RASs [1, 2]. However, source capsules with multi-millimeter diameters are too large to treat tumors in geometrically constrained or neurologically sensitive locations such as brain tumors.

The Californium Program at Oak Ridge National Laboratory (ORNL), in collaboration with Isotron, Inc., is developing a family of miniature HDR ^{252}Cf sources that will be coupled to Isotron's source delivery system. Isotron's Neutron Brachytherapy (NBT™) System will prove vastly superior to existing treatments, primarily through its ability to kill oxic (oxygenated), hypoxic, and radioresistant cancer cells. Conventional gamma and X-ray-based radiation sources have proven ineffective in destroying hypoxic and radioresistant cells found at the core of Stage III/IV tumors. These radioresistant cancers exist in melanoma, sarcoma, gliomas, adenocarcinoma of the prostate, locally advanced breast cancer, cervical cancer, and cancers of the head, neck, and oral cavity. Isotron's system will be able to treat many advanced-stage cancer patients currently considered untreatable, offering hope for patients with these devastating diseases.

These HDR sources can either be used alone or augmented with the addition of one or more boronated pharmaceuticals. These compounds are designed to preferentially accumulate in malignant tumor cells actively dividing along the periphery of the tumor margins. When a boron-loaded cell is irradiated with neutrons, neutron capture via the reaction $^{10}B(n,\alpha)^{7}Li$ deposits sufficient energy to kill the cell with minimal effect on the neighboring healthy cells that contain little or no boron. This enhancement will render the NBT™ System even more effective in killing cancer cells.

DESCRIPTION OF WORK

Medical sources fabricated at ORNL contain a cermet wire consisting of californium oxide in a palladium matrix. This wire is produced by coprecipitating californium oxalate and palladium, calcining the oxalate to the oxide, melting into a cermet pellet, then rolling the pellet into a wire using a jeweler's rolling mill [3]. The standard wire form is a modified square wire (with rounded corners) with a cross-sectional diagonal of ~1.3 mm and linear loadings of ~20 μg/mm. However, in 2000, a customized rolling mill was developed and tested at ORNL and the first submillimeter ^{252}Cf wire was produced. The capsules for the miniature medical sources were designed around this wire. New radioactive source designs are required to undergo special form testing to ensure their integrity under standard accident conditions for transportation purposes [4]. A protocol has been developed to demonstrate nonleakage of contents after special form testing by nonradioactive means. Hardware and process improvements have been developed which should enable continued reduction of cermet wire diameter for further miniaturization of sources.

RESULTS

Cermet wire produced with the new rolling mill contained the highest volumetric ^{252}Cf loading to date: several hundred micrograms per cubic millimeter of wire. Rolling the wire as small as possible is very tedious, and one handling mistake can ruin days of work. Tooling has been developed to permit further reduction of wire diameter to facilitate insertion into the miniature capsules. After final wire sizing, a segment will be cut to length; inserted into the capsule; and welded, using a welder that has been customdesigned for remote use in a hot cell environment. After decontamination and assay for neutron intensity, the sources will be demonstrated to be leak tight, the cable attached, and the sources prepared for shipment. Demonstration of these processes has already been completed.

One approach to special form testing of source integrity is to fabricate sources with tracer levels of the radioactive material. For ^{252}Cf sources, this would require not only complete in-cell fabrication and decontamination but also development of out-of-cell capabilities for potentially destructive tests on these radioactive sources. To circumvent this effort, a protocol has been developed using terbium as a nonradioactive surrogate for californium within dummy cermet wire. This wire can be welded inside the capsules, which are then subjected to the special form testing requirements. Nonrelease of capsule contents is demonstrated by a hot-water leach of the capsule, followed by terbium analysis using inductively coupled plasma–mass spectrometry. The sensitivity of this technique is comparable to the release limits specified for analysis by radioanalytical counting methods.

As designed, these miniature HDR prototype sources will far surpass the intensity of existing sources with comparable capsule dimensions. Prototype sources will be fabricated at ORNL for distribution and clinical testing in conjunction with Isotron's NBT™ System. Ongoing testing by Isotron of boron-enhanced ^{252}Cf brachytherapy promises improved therapeutic efficacy, especially for high-grade gliomas (e.g., glioblastoma multiforme).

REFERENCES

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