DEVELOPMENT OF MINIATURE HIGH-DOSE-RATE ^{252}Cf SOURCES FOR BORON-ENHANCED AND FAST NEUTRON BRACHYTHERAPY.

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ABSTRACT: Californium-252 radioisotopic neutron source capsules have been used for brachytherapy treatment of tumors for nearly 30 years. In the United States, several manually afterloaded low-dose-rate (LDR) source designs have been produced; internationally, only four remotely afterloaded high-dose-rate (HDR) systems are known to have been demonstrated. These HDR systems typically used source capsules with diameters of several millimeters, which restricted their application in treating tumors in geometrically constrained or neurologically sensitive locations. The Californium Program at Oak Ridge National Laboratory (ORNL), in collaboration with Isotron, Inc., is developing a family of miniature HDR ^{252}Cf source designs that will be coupled to a remote afterloader system (RAS) for treatment of a variety of tumors. Providing an HDR brachytherapy source with dimensions significantly smaller than comparable HDR sources will enable unprecedented treatments of radioresistant cancers. Such cancers exist in melanomas; sarcomas; gliomas; tumors of the salivary glands; adenocarcinomas of the prostate; locally advanced breast cancer; cervical cancer; and cancers of the head, neck, and oral cavity. These sources can either be used for stand-alone fast neutron brachytherapy or be coupled with boronated pharmaceuticals for boron-enhanced neutron brachytherapy.

KEY WORDS: Cf-252, californium, neutrons, brachytherapy, fast neutron therapy, boron-enhanced brachytherapy

INTRODUCTION: The effectiveness of ^{252}Cf neutron brachytherapy in treating radioresistant (bulky and/or hypoxic) tumors has been demonstrated over three decades of clinical trials. Neutron brachytherapy has certain radiobiological advantages over external beam therapy, in particular the reduction of dose as the square of the distance from the source. This attenuation delivers maximum dose to the central tumorous region while sparing healthy tissue farther from the source. Another practical advantage is that thermalization of the fast neutrons permits coupling of fast neutron and boron capture therapy, which can enhance the neutron dose to metastases at several centimeters from the source.

Two technical issues have hindered widespread application of ^{252}Cf neutron sources for cancer therapy: (1) the dichotomy between small source diameter and high neutron intensity and (2) the availability of commercial RASs coupled to appropriately sized sources. For maximum radiobiological advantage and minimum treatment times, HDR ^{252}Cf sources are required. However, the potential for significant dose to clinical personnel (1 μg of ^{252}Cf delivers 0.022-mSv/h fast neutron and 0.0019-mSv/h gamma dose equivalent at 1 m in air) requires remote afterloading of HDR sources. HDR neutron sources to date have required an outer source diameter of ~3 mm, too large for effective treatment of tumors with limited accessibility such as glioblastomas. Sources as small as 0.8 mm in diameter have been reported[1], but are limited to a loading of 3 μg of ^{252}Cf (see Table 1). Reported Russian LDR medical sources containing up to ~30 μg of ^{252}Cf are available for interstitial therapy in configurations with diameters of ~1.2 mm and various lengths, while their standard HDR source is listed as containing up to 2137 μg of ^{252}Cf in a 3-mm-diameter capsule[1]. In comparison, the standard U.S. medical source is a 2.8-mm-diameter by 23-mm-long capsule containing up to 30 μg of ^{252}Cf, although source fabrication technology that can load several milligrams into this capsule geometry has been demonstrated[2].

All U.S. source designs have been limited to manually afterloaded LDR brachytherapy, except for one HDR source (4.7-mm diameter and maximum ^{252}Cf loading of 1025 μg) developed for a Toshiba RAS[3]. This

Table 1. Representative Existing Source Designs for ^{252}Cf Brachytherapy

Source	Diam. (mm)	Max. ^{252}Cf content[a] (μg)	Specific loading[b] (μg/mm^3)
NC252M31[c]	0.8[d]	3.0	0.9
SALC[e]	1.0[f]	2.4	0.2
NC252M23[c]	1.3[d]	29.9	1.4
AT[e]	2.8[f]	29.8	0.2
NC252M41[c]	3.0[f]	2137.	20.1
TALC-PC[e]	4.7[f]	1025.	6.0

[a]Maximum determined by source license registry.
[b]Maximum ^{252}Cf content per total capsule volume.
[c]Russian design.
[d]Single encapsulation.
[e]U.S. design.
[f]Double encapsulation.

afterloader was used for intracavitary treatments and skin cancer teletherapy, but is no longer in operation. The most widely used RAS is a Russian design[4] deployed in Moscow and Lithuania which uses the 3-mm-diameter HDR source design. Indigenous remote afterloaders are reported to be in use in the Czech Republic[5] and, more recently, in China[6]. No coupled HDR source–RAS design has been reported that is appropriate for general application to interstitial therapy such as that for glioblastomas.

MATERIALS AND METHODS: All U.S. medical source designs were developed in the 1970s at the Savannah River Laboratory (SRL)[7]. Since then, the ^{252}Cf source fabrication program has been relocated to ORNL, and the first medical sources fabricated at ORNL in 1998 were based on an SRL design. The SRL-fabricated sources used a cermet core wire (Cf_2O_3 embedded in a palladium matrix) enclosed in a Pt-Ir-alloy sheath, with the wires drawn through a die to diameters as small as 0.3 mm. However, these small wires as encapsulated were limited to linear loadings of <1 μg/mm.

ORNL pursued the unclad cermet wire source form, produced by rolling a melted cermet pellet into a long wire using a jeweler's rolling mill. Details are available in Ref. 2. 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 ~200 μg/mm. Until recently, the thinnest wires fabricated at ORNL exceeded 1 mm in diagonal dimension. A customized rolling mill was recently developed and tested at ORNL; the first submillimeter ^{252}Cf core wire was produced earlier this year.

RESULTS AND DISCUSSION: The cermet wire produced with this new rolling mill contained the highest volumetric ^{252}Cf loading ever reported—in the range of several hundred micrograms per cubic millimeter of wire. Whether these results represent an upper limit to cermet volumetric loading has not been determined. Source capsules have been designed to encapsulate this wire into the first miniature HDR ^{252}Cf sources. Using a figure of merit of encapsulated ^{252}Cf mass per total capsule volume (Table 1), these prototype sources will approach a twofold increase in volumetric loading over that of currently available sources in a significantly reduced capsule geometry. Special form testing of these new capsule designs is required to obtain regulatory compliance for leak-tight capsule integrity. Prototype sources will be fabricated at ORNL for distribution and clinical testing. These sources are designed to couple with an RAS designed by Isotron, Inc., for practical clinical handling. Fabrication associated with further source miniaturization is also ongoing to broaden the potential range of interstitial applications.

These HDR sources are appropriate for stand-alone brachytherapy. However, brachytherapy in conjunction with boron pharmaceuticals, to gain boron enhancement of the brachytherapy dose, can effectively utilize the technology developed over the years in support of external beam boron neutron capture therapy. One study[8] of the potential for boron enhancement of brachytherapy dose concluded that for a ^{10}B concentration of 50 ppm in the tumor, the dose to the tumor would be augmented by 3.4% at 1 cm from the ^{252}Cf source, 7.7% at 5 cm, and 23.1% at 10 cm. The dose enhancement scales approximately linearly with ^{10}B concentration. Isotron has developed its own computer model to study the dose enhancement factor based on the presence of boron compounds. Boron-enhanced ^{252}Cf brachytherapy promises improved tumor control by providing a capability for tailoring the dose distribution around the region of the tumor and enhancing dose delivery to neighboring metastases.

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