U.S. Nuclear Regulatory Commission (NRC)
Advisory Committee on the Medical Uses of Isotopes (ACMUI)

Subcommittee on Y-90 Microsphere Medical Events

Final Report
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Subcommittee Members
Vasken Dilsizian, MD
Josh Mailman
Melissa Martin
Michael O'Hara, PhD (Chair)
Megan Shober

Consultant to the Subcommittee: John F. Angle, MD
NRC Staff Resource: Katie Tapp, PhD

Charge

The ACMUI Chair, Darlene Metter, MD, established this Subcommittee on October 4, 2021 during the ACMUI 2021 Fall Meeting to evaluate the issue of Y-90 microsphere medical events in more depth and, in consultation with the vendors, propose methods to decrease the number of Y-90 microsphere medical events.

Subcommittee Process

The subcommittee identified three factors which contributed to avoidable medical events (MEs): 1) low frequency of administration, 2) errors in treatment planning, and 3) workflow time challenges during the procedure that ensure that all elements of the treatment are in accordance with the written directive. Based on these factors, the subcommittee proposes three actions to prevent future MEs.

The vendors that currently provide yttrium (Y)-90 microspheres in the United States (Boston Scientific and Sirtex Medical) were approached for their input on the proposed recommendations. The subcommittee received written and verbal input from both companies. The Subcommittee concluded that implementing the proposed recommendations would have a positive impact on radiation safety for microsphere users.

Subcommittee Recommendations

The following recommendations can be used by the NRC and the vendors to serve as additional learning tools for licensees. The Subcommittee recommends that the NRC have additional conversations with the vendors to understand how the vendor programs impact MEs and issue an information notice to alert users to events that occurred in the past that could have been prevented by these measures. Furthermore, the NRC or the ACMUI should also consider publishing a journal article or give a presentation at a national meeting to reach licensees.

1. On a regular basis, licensees should review the mechanics of Y-90 microsphere delivery and setup procedures as described by the manufacturer.

2. Licensees should confirm all data and calculations in the treatment plan, prior to administration.
3. Licensees should use a "time out" to assure all elements of the administration are in accordance with the written directive. Elements such as conformation of the patient's name, treatment location and dosage comparison to the written directive.

Background

Hepatic radioembolization or selective internal radiation therapy (SIRT) is the intravascular administration of labeled glass or resin microspheres into the hepatic artery to deliver a radiation dose to a tumor target within the liver. Hepatic radioembolization currently uses Y-90 labeled microspheres for the treatment of primary and metastatic malignancies of the liver. Two vendors are currently approved by the U.S. Food and Drug Administration for treatment of liver tumors with Y-90 microspheres. TheraSphere™ from Boston Scientific is approved to treat hepatocellular carcinoma and SIR-Spheres® from Sirtex Medical is approved to treat metastatic colorectal tumors of the liver. During the past few years, both vendors have increased their hepatic radioembolization business by approximately twenty percent. Similar to past years, the MEs reported during 2020 were low compared to the number of treatments performed.

The ACMUI Medical Events Subcommittee Report from October 2021 shows that MEs involving Y-90 administration continues to be the most common ME (Agencywide Documents Access and Management System Accession No. ML21288A127).

Radioactive Source	Total ME over 4 Years
Manual Brachytherapy	31
Remote Afterloader, Teletherapy, Gamma Stereotactic unit	41
Intravascular Cardiac Brachytherapy	5
Gamma Knife Perfexion + Icon	5
Y-90 Microspheres (combined)	93

The types of MEs for Y-90 microspheres included: >20% residual activity remaining in the delivery device, delivery device setup error, wrong dose given (treatment plan calculation error), wrong site treated (catheter placement error), wrong dose vial selected and wrong site. In 2020, 80% of the MEs for TheraSphere™ and 100% for SIR-Spheres® may have been influenced by infrequent performance of the treatment procedure and inattention during the procedure. A past ACMUI MEs Subcommittee noted that performance of a time out and use of a checklist immediately before administration of byproduct material could have prevented some MEs. The ME subcommittee proposed actions to prevent Y-90 microsphere MEs that included review the mechanics of Y-90 microsphere delivery devices and setup procedures, confirm all data and calculations in the treatment plan and perform a time out at the beginning of each procedure to assure all elements of the treatment are in accordance with the written directive. The ME subcommittee also proposed some possible elements of a time out that include identity of the patient via two identifiers (e.g., name and date of birth), procedure to be performed, isotope, activity, second check of dosage calculation and that the written directive and dosage to be delivered are identical as well other elements that may be applicable. In response, the NRC staff issued information notice 19-07, "Methods to Prevent Medical Events," to inform licensees of these ACMUI recommendations (ML19240A450).

Vendor Consultation

Introduction

Addressing MEs involving the administration of Y-90 microspheres may be facilitated by collaboration with vendors. The ACMUI created this subcommittee to evaluate this issue in conjunction with the vendors of Y-90 microspheres. There are currently two Y-90 microsphere vendors in the United States, Boston Scientific (TheraSphere™) and Sirtex Medical (SIR-Spheres®). The subcommittee contacted both vendors for assistance with this evaluation. Both vendors were given copies of the MEs Committee report presented at the ACMUI meeting on October 4, 2021, general questions to start the conversation, and the ACMUI's proposed three actions to prevent Y-90 microsphere MEs. The vendors were specifically asked if these proposed actions to prevent Y-90 microsphere MEs are appropriate and if there are further actions that will help to reduce the number of MEs. Teleconferences were held on April 20, 2022, with Sirtex Medical and on May 26, 2022, with Boston Scientific.

Sirtex Medical

Sirtex Medical has developed programs and taken steps that they believe will reduce MEs and increase the safe and effective use of SIR-Spheres®. In response to the Y-90 Microspheres Subcommittee's request, Sirtex Medical evaluated the MEs reported by licensees between 2017-2020 described in the 2021 ME Subcommittee report. Their evaluation identified four causes of MEs associated with SIR-Spheres®, which were:

1. Greater than 20% residual activity remaining in the delivery device not due to stasis,
2. The wrong dose given (treatment plan calculation error),
3. The wrong site treated (catheter placement error), and
4. The wrong site (written directive error).

Sirtex Medical agreed that greater use of the ACMUI recommendations 1-3 by licensees may prevent MEs related to licensee set up of the device and procedural errors.

One action the vendor has taken to prevent MEs was to develop a SIR-Spheres® Microspheres Activity Calculator. This may serve as second check against the activity identified in the written directive. The accuracy of these types of spreadsheet calculators should be confirmed by Sirtex Medical, tested by licensees and reviewed by the Medical Team at the NRC.

Another action the vendor mentioned was the SIR-Spheres® Training Evaluation Certification Program. This purpose of this program is to ensure that Sirtex Medical's Y-90 microspheres licensees have the infrastructure in place to use radioactive microspheres. This program includes guidance that all necessary nuclear medicine and radiation safety support equipment and personnel are in place and the licensee has sufficient arteriography capabilities. It also includes In-Service site visits from Sirtex Medical's multidisciplinary team for assistance with all of microsphere implantation components and training of the treatment physician and radiation safety officer. In addition, the vendor cited that the vendor proctor's assessment is another action to prevent MEs. The proctor can recommend additional proctoring sessions for treating physicians and institutions before being qualified by Sirtex to use SIR-Spheres®. There is also a minimum frequency of treatments with SIR-Spheres® necessary for continued SIR-Spheres® use according to the vendor. Sirtex Medical has also increased the case coverage in their Supplemental Training program to combat MEs by putting more of the vendor's experienced staff in closer contact with the users of their Y-90 microspheres.

Further Discussion with Sirtex Medical

Further discussion between Sirtex Medical and the Medical Team at the NRC is necessary to further understand how Sirtex Medical's programs outlined here affect MEs, how the vendor judges the effectiveness of these programs and how the vendor tests the accuracy of spreadsheet tools to calculate activity. After reviewing the ME events report for 2021 (ML22112A104) from the Medical Radiation Safety Team at NRC, the vendor identified clogged microcatheters as approximately 30% of the MEs. In addition, the NRC staff should understand the steps, if any, that the vendor is taking to limit the impact of clogged microcatheters.

Boston Scientific

Boston Scientific has developed programs and products that they believe will reduce MEs and increase safe and effective use of TheraSphere™. The vendor's post market surveillance program monitors all complaints and responds when a potential trend emerges. This review process includes reviewing the NRC database for TheraSphere™ related MEs to determine the root cause of the medical event and take action to minimize its frequency and severity.

In response to the Y-90 Microspheres Subcommittee's request, Boston re-analyzed the 59 MEs NRC identified from 2017 to 2020. They calculated the rate of NRC reported MEs per volume of dose vials shipped within each year and identified the rate of reported MEs is much less than one percent of volume of dose vials shipped. In addition, the rate of MEs has decreased during this time when compared to the increase in volume of dose vials shipped.

The vendor pointed to possible actions while responding to the questions that the Subcommittee used to open the discussion. Many of these actions the licensee already has at their disposal. For example, leaving >20% volume of TheraSphere™ in the delivery device may need improved quality systems or events related to the delivery device may need enhancements to the written directive and/or increased familiarization with the device. Software tools or checklists could be used to improve issues like the wrong dose given due to calculation errors, catheter placement errors or selection of the wrong dose vial. Greater use of the ACMUI proposed actions to prevent MEs will also possibly reduce these issues.

Boston Scientific provides resources to aid in the planning and facilitation of TheraSphere™ Y-90 treatments. The resources include the TheraSphere™ Instructions for Use which is supported by training at new sites for physician authorized users, radiation safety officers and support staff and software tools to assist customers in treatment planning and ordering TheraSphere™. The software tools include: TheraSphere™ Now, TheraSphere™ Treatment Window Illustrator, and TheraSphere™ iDOC.

TheraSphere™ Now is an online ordering tool that notifies users of potential order errors at the time of the order. The vendor informed the Subcommittee that approximately 50% of TheraSphere™ users currently use this tool.

TheraSphere™ Treatment Window Illustrator is a spreadsheet-based tool that can assist users with ordering the appropriate dose size based upon the desired absorbed dose, timing of administration, lung shunt fraction, dose to the lungs, and anticipated residual waste.

TheraSphere™ iDOC is an online interactive dose ordering calculator that can assist users in calculating and ordering the appropriate TheraSphere™ dose vial size.

The optional TheraSphere™ Administration Checklist instructs users to confirm patient identity, instructions for administration set priming, dose vial preparation, administration set assembly with the dose vial, final assembly immediately before administration, TheraSphere® administration and disassembly and cleanup. The vendor believes appropriate use all these tools could reduce MEs.

Further Discussion with Boston Scientific

Further discussion between Boston Scientific and the Medical Team at the NRC is necessary to fully understand how the vendor's programs outlined here affect MEs, how the vendor judges the effectiveness of these programs and how the vendor tests the accuracy of spreadsheet and software tools. Specifically, are MEs lower at licensed facilities that use Boston Scientific's spreadsheet/ software tools? In addition, the NRC staff should understand the steps the vendor is taking, if any, to limit the impact of clogged microcatheters.

Summary

The vendors have embraced the ACMUI proposed actions to prevent Y-90 MEs. However, the vendors should include these actions in their training of new users, interactions with current users and in discussion of MEs with any user. The Subcommittee believes that the NRC should embrace these three proposed actions to prevent Y-90 MEs to ensure that all Y-90 microsphere users are aware of their utility.

The use of spreadsheets, checklists, and software tools appear to be methods the vendors have employed to reduce errors in Y-90 isotope ordering, selection of the wrong dose vial, calculation errors, and to reduce the errors during Y-90 procedures. These tools can assist the end user to order Y-90 and properly administer the therapy. The accuracy of these tools is unclear and should be investigated more fully.

Recommendations

The NRC should evaluate the utility of the software programs and checklists provided by the microsphere vendors. A regular review of these tools can improve the licensees understanding of these software devices, assist vendors with further development of these tools, and potentially catch inconsistencies between vendors and with NRC regulations and recommendations.

In addition, the NRC should issue information notices to alert licensees of MEs and, where possible, make recommendations and suggest measures licensees can take to prevent similar events in the future. These recommendations can be used by the NRC and the vendors to serve as additional learning tools to prevent MEs.

In summary, the three recommendations for licensees are as follows:

1. On a regular basis, licensees should review the mechanics of Y-90 microsphere delivery and setup procedures as described by the manufacturer.
2. Licensees should confirm all data and calculations in the treatment plan, prior to administration.
3. Licensees should use a "time out" to assure all elements of the administration are in accordance with the written directive. Elements such as conformation of the patient's name, treatment location and dosage comparison to the written directive.

References

January 24, 2022, Email to Boston Scientific

January 24, 2022, Email to Sirtex Medical

April 20, 2022, 35.1000 Y-90 Microsphere Medical Event Review by Sirtex Medical

March 23, 2022, letter to Michael O'Hara from Boston Scientific

April 20, 2022, Presentation entitled "35.100 Y-90 Microsphere Medical Events Review" from Sirtex Medical

Respectfully submitted,

Subcommittee on Y-90 Microsphere Medical Events
Advisory Committee on the Medical Uses of Isotopes
U.S. Nuclear Regulatory Commission

The ACMUI unanimously approved this report as presented during its public meeting on December 5th, 2022.