Advisory Committee on the Medical Use of Isotopes (ACMUI)

Comments on the current requirement of 700 hours for training and experience for authorized users of alpha and beta emitters

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Charge: To determine if the current requirement of 700 hours for training and experience for authorized users of alpha and beta emitters, in 10CFR 35.390 (Training for use of unsealed byproduct material for which a written directive is required), places hardship on the patient community and to make recommendations for ACMUI action.

Summary: Radiolabeled antibody treatment of lymphoma with beta emitters was approved by the United States Food and Drug Administration more than 12 years ago. At one time there were two agents were available: yittrium-90 ibritumomab Tiuexetan (Zevalin®) and iodine-131 tositumomab (Bexxar®). Use of both agents peaked within a few years after their introduction but, despite favorable clinical results, has decreased steadily since then. Bexxar®, in fact, was withdrawn from the market in 2014, when fewer than 75 patients received the drug. The explanation for decreasing use of these agents, and the discontinuation of one of them, is multifactorial. One factor is cost. A 2007 survey by the Society of Nuclear Medicine (now the Society of Nuclear Medicine and Molecular Imaging) found that Zevalin® cost hospitals $22,000 -$24,000 per treatment, while Medicare's planned reimbursement was only $21,850 and even less for Bexxar®. Another factor is competition from other effective therapies, which do not use radiation, that were developed after Zevalin® and Bexxar® were introduced. A lack of familiarity with these agents is another obstacle to their widespread use. Hematology/oncology fellows are not exposed to these radiopharmaceuticals during training.

Another possible explanation, one that this subcommittee has been charged to investigate, is a shortage of authorized users (AUs) that has arisen because of the requirement for 700 hours of training and experience to obtain AU status which went into effect shortly after these agents were introduced. It is difficult to gauge the impact of a lack of AUs because even at large medical centers where there is an abundance of clinicians and AUs who work closely together, these radiopharmaceuticals are used infrequently. For example, at Memorial Sloan Kettering Cancer Center in New York, an institution dedicated almost exclusively to the care of patients with malignancy, a total of 190 patients were treated with radiolabeled antibodies (80 Zevalin®, 110 Bexxar®) between 2009 and 2014. At the Kettering Medical Center in Dayton, Ohio, only three patients have been treated over the past nine years. At the University of Maryland, 25

patients have been treated with Zevalin since the drug was approved in 2002. In the North Shore Long Island Jewish Health System, one of the largest healthcare systems in the country, an average of 5 patients per year were treated between 2005 and 2014. At Washington University and Barnes-Jewish Hospital Radiation Oncology in St. Louis, 55 patients were treated with radiolabeled antibodies between 2004 and 2014.

In summary, the explanation for the infrequent and steadily decreasing use of radiopharmaceuticals for the treatment of lymphoma is due to many factors. Based on the information available at this time, the subcommittee is not able to determine whether this can be attributed to a shortage of AUs, if there is one, caused by the current T&E requirements.

Although the subcommittee's review has focused on radiolabeled antibody therapy for lymphoma, there is another therapeutic radiopharmaceutical that should be mentioned. In 2013, the alpha emitter radium-223 dichloride (Xofigo®) was approved for treatment of castrate resistant prostate carcinoma with symptomatic bone metastases and no known visceral metastases. Since this agent was introduced only about two years ago, no trending data are yet available and factors affecting its use cannot be addressed.

Recommendation: The subcommittee requests to continue pursuing this charge with recommendations to be presented at the spring 2016 ACMUI meeting.