ACMUI Sub-Committee Draft Report on Training & Experience For Authorized Users of Alpha and Beta Emitters under 10 CFR 35.390

Submitted on March 10, 2016

Nuclear Regulatory Commission (NRC)
Advisory Committee on the Medical Uses of Isotopes (ACMUI)
Report on Training & Experience for Authorized Users of Alpha and Beta Emitters under 10 CFR 35.390

Sub-Committee Members: V. Dilsizian M.D., R. Ennis M.D., S. Langhorst Ph.D., C. Palestro, M.D. (chair), L. Weil, P. Zanzonico, Ph.D.

Introduction

The Sub-Committee on Training & Experience for Authorized Users was charged with the following tasks:

1. To determine if the current requirement of 700 hours for training and experience for authorized users (AU) 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.

2. To establish a recommendation for the total number of hours of T&E for authorized users of such emitters that appropriately balances safety with reasonable patient access to these agents.

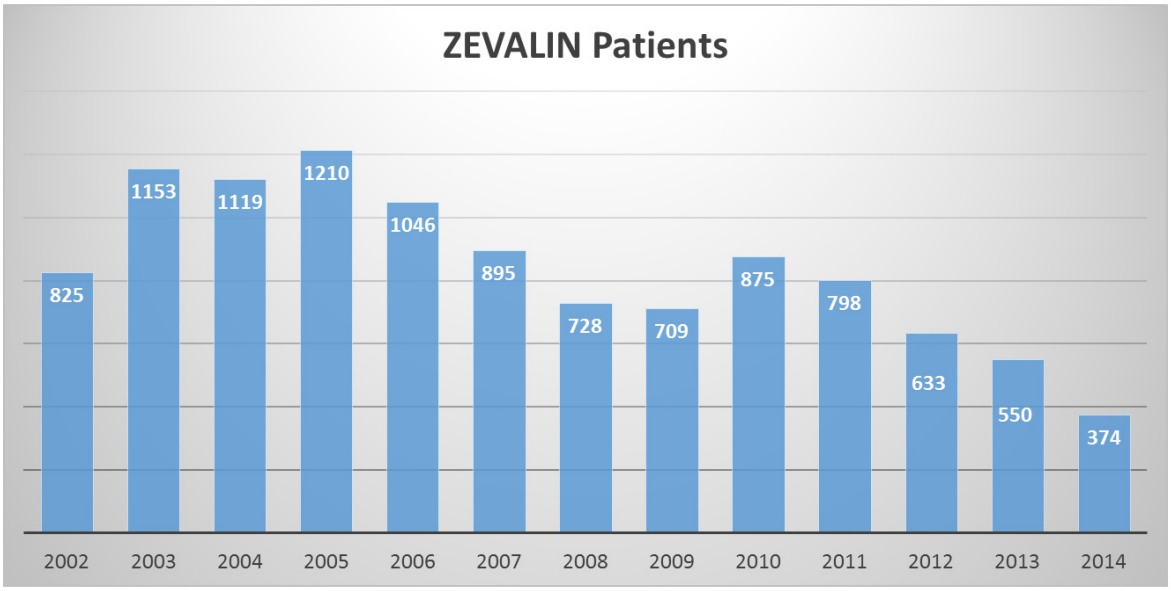
ACMUI Sub-Committee Draft Report on Training & Experience For Authorized Users of Alpha and Beta Emitters under 10 CFR 35.390

Submitted on March 10, 2016

Charge 1:

Background: Radiolabeled antibody treatment of lymphoma with beta emitters was approved by the U. S. FDA approximately 14 years ago. Two agents initially were available: yittrium-90 ibritumomab tiuexetan (Zevalin®) and iodine-131 tositumomab (Bexxar®). Use of both agents, which peaked a few years after introduction, has, despite favorable clinical results, steadily declined since (Figure 1). Bexxar®, in fact, was withdrawn from the market in 2014, because of a lack of use (fewer than 75 patients treated in 2014).

FIGURE 1



(Adapted from Spectrum Pharmaceuticals, ACMUI meeting October 2015)

The subcommittee examined the factors that could possibly account for the decrease in use of these agents.

Lack of knowledge: According to Dr. Cultrera' s presentation at the Fall 205 ACMUI meeting, hematology/oncology fellows are not exposed to these agents during their training so they may not be aware that these agents are available and consequently do not prescribe them. This is an educational, not a regulatory issue.

Competition: Since these agents were introduced about 14 years ago, new, effective, therapies that do not involve radiation have been developed, and it likely that some of the decrease in use is related to the availability of these newer agents. This is not unique to radiolabeled antibodies; this is common to all drugs: as newer, equally or more effective, agents become available, the use of older agents declines.

Shortage of Authorized Users: It has been suggested that the infrequent and declining use of these agents is a direct result of the requirement for 700 hours of training and experience to obtain Authorized User (AU) status that went into effect shortly after these agents were introduced. In his letter of 1/25/2016 to the ACMUI, Dr. Joseph Mace states that to his knowledge, "… no oncologist has been able to receive AU status under the alternate pathway, since the regulations went into effect…" Without knowledge of how many oncologists sought AU status prior to the rule change, it is not possible to assess the significance of this statement. The only way to determine the impact on AU's that the change in T&E requirements had, would be to have aggregate data on AU's over time, data, which unfortunately, are not available.

These considerations, it would appear, provide at least prima facie evidence that lack of clinical use of Bexxar® and Zevalin® is not due to a lack of AUs.

The assertion that a shortage of AUs is the cause of the decline in the use of these agents is undermined by the fact that even at many large medical centers with an abundance of clinicians and AUs who work closely together, these radiopharmaceuticals are used infrequently (Figure 2). According to his January 2015 letter, Dr. Mace, who receives consultations from "across the state of Florida" has administered beta emitters, including Zevalin® to more than 40 patients over the past decade, or only about 4 per year.

FIGURE 2

Institution	Time Period	Total number of Therapies
Memorial Sloan Kettering Cancer Ctr. (NY)	2009-2014	190
University of Maryland (Baltimore)	2002-2014	25
North Shore LIJ Health System (NY)	2005-2014	49
Washington University/Barnes-Jewish Hospital (St. Louis)	2004-2014	55

(Adapted from Palestro, presented at the ACMUI meeting Oct 2015)

Safety: The exceptional safety record that has accompanied beta, and more recently alpha emitting radiopharmaceuticals, is indisputable. Therefore why not reduce the T&E requirements anyway, regardless of whether or not there is a shortage of AU's? It is important to note that the excellent safety records achieved with these agents have been attained, in the majority of cases, by or in conjunction with, AU's who have successfully completed the rigorous T&E requirements.

SUMMARY:

The ramifications of a change in T&E are potentially significant. In terms of safety, as already noted, the excellent safety records achieved with these agents have been attained, for the most part, by or in conjunction with AU's who have successfully completed the rigorous T&E requirements. Whether or not the safety records would be comparable in the hands of AU's with considerably less T&E is a matter of conjecture. It has been suggested that 80 hours of T&E is sufficient for administration of these agents. This is based on the concept that if 80 hours of T&E is sufficient for radioactive iodine administration which, it has been asserted, is far more complex and hazardous, then a comparable amount of T&E is sufficient for administration of alpha & beta emitters. It is important to note that the field of Nuclear Medicine, including therapy, originated to a great extent in endocrinology, because of the role of radioactive iodine in the diagnosis and treatment of thyroid disease. Thus endocrinologists have a long history of familiarity with the use of radioactive materials.

Virtually all of the letters in support of a change in T&E support this change for oncologists. Surely there are other individuals, in other specialties, who are capable of administering these agents; should they also be included? Finally, should satisfactory completion of T&E allow an individual to administer all of these agents, or should use be restricted to specific radiopharmaceuticals as suggested in the February 9th, 2016 letter of Hilliard et al. to the ACMUI?

Since it is not possible to conclude that the current T&E requirements are the only, or even the principal, cause of the decreased use of radiopharmaceuticals like Zevalin® and Bexxar®, and because of the potential issues raised by the proposed changes in T&E, the subcommittee recommends against the reduction in the number of hours of T&E required for 10 CFR 35.396 use.

Charge 2:

Establish a recommendation for the total number of hours of T&E for authorized users of alpha and beta emitters to ensure safety.

While, for the reasons stated, the subcommittee opposes the reduction in the number of hours of T&E, we also recognize the need for a thorough review of the current T&E requirements. One important reason for this review is that is has been nearly 15 years since the current requirements were established. Since that time new radiopharmaceuticals have been

introduced and this is a trend that likely will continue. Appropriate T&E requirements for these agents need to be established.

There is another important reason to undertake this review. The educational paradigm has changed over time. There has been a shift away from prescriptive curricula (i.e. specific number of classroom hours) to competency-based education. The time has come to reevaluate our educational approach to T&E, with an emphasis on competency, not just experience.

This undertaking is complicated and cannot be completed in weeks or even months. It requires input from many stakeholders, if it is to be successful. Once established, the T&E requirements need regular, periodic review, to ensure that they are current.

Therefore the subcommittee recommends that the ACMUI establish a standing subcommittee with the specific charge of periodically reviewing the T&E requirements currently in effect and making recommendations for changes as warranted.

Endorsement

This report was unanimously approved by the subcommittee on February 24, 2016. However, a differing opinion with respect to the barriers to access follows:

I support the Subcommittee's assertion that the Training and Experience requirements need to be reviewed and re-evaluated. But I do not agree that the current requirements do not effectively create some barriers to access to care.

As the Subcommittee Report states, the 700 hour Training and Experience requirement for AUs of alpha and beta emitters is surely not the primary reason why these agents are not frequently used in many major medical centers. There is no shortage of clinicians available and authorized to administer these radiopharmaceuticals, and other factors must contribute to the lack of utilization.

It is important to acknowledge that this condition may not hold true for the community setting, where NHL patients often receive treatment. NHL patients often live with the disease for many years, and require a varied armamentarium of therapies to address each subsequent recurrence. Many of these patients are elderly, unable to travel, have very limiting medical insurance networks, and may be too frail to tolerate the debilitating side effects of cytotoxic therapies. To assert that all patients have access to RIT is to ignore the logistical barriers that exist for those who are limited to receiving therapy in the rural or community setting. The 700 hour T&E requirement effectively limits AUs to those medical specialties that cover the requirements in residency training. Those specialists may simply not be available in the community setting, creating a real

barrier to access for those patients who are unable to seek treatment in a larger medical center.

Respectfully submitted,

Laura Weil, ACMUI Patients' Rights Advocate