Diversification of ^{99}Mo/^{99m}Tc Supply

The article by Bénard et al. in this month's issue of *The Journal of Nuclear Medicine* (*1*) is an important work, showing the feasibility of producing large quantities of ^{99m}Tc on a biomedical cyclotron and extraction of the ^{99m}Tc from the target material, converting it to a chemical form suitable for conventional compounding of nuclear medicine drugs. The authors state "with some modifications of existing cyclotron infrastructure, this approach can be used to implement a decentralized medical isotope production model. This method eliminates the need for enriched uranium and the radioactive waste associated with the processing of uranium targets." The recent planned and unplanned shutdowns of nuclear reactors producing ^{99}Mo highlight the need for alternative production methods, necessitating a review of the current state of ^{99}Mo/^{99m}Tc production and the potential alternatives moving forward to ensure a steady, uninterrupted supply of ^{99}Mo/^{99m}Tc for decades to come.

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CONVERSION EFFORTS FROM HIGHLY ENRICHED URANIUM (HEU) TO LOW-ENRICHED URANIUM (LEU)

Currently, 85%–95% of the world's ^{99}Mo is produced using HEU. The United States is the world's primary supplier of HEU, which has an enrichment of 93%. The U.S. Department of Energy's National Nuclear Security Administration has, with cooperation from all of the current commercial producers, set a goal of total conversion from HEU to LEU by 2016. ANSTO (Australia) and NTP Radioisotopes (South Africa) already use LEU for their ^{99}Mo production. Mallinckrodt (The Netherlands) and IRE (Belgium) are in the process of shifting their ^{99}Mo production from HEU to LEU and plan to have the conversion complete by the end of 2015. The AECL (Canada) has decided to exit the market, stating that the cost of maintenance and conversion to LEU production at the Chalk River reactor is too high for staying in the market. AECL currently provides 31% of the world's ^{99}Mo; alternative production methods will be needed.

ALTERNATIVE PRODUCTION OF ^{99}Mo

There are currently 3 companies working on alternative production methods for ^{99}Mo: Babcock & Wilcox, SHINE Medical Technologies, and NorthStar Medical Radioisotopes.

Babcock & Wilcox has suggested a series of small, subcritical liquid fuel reactors with LEU solution to produce ^{99}Mo. The ^{99}Mo is extracted from the LEU solution and can be used with the existing ^{99}Mo/^{99m}Tc generator model. This project is currently suspended, as Babcock & Wilcox is seeking a new partner.

SHINE Medical Technologies uses a subcritical reactor and deuterium–tritium beam line to bombard an LEU solution with neutrons. SHINE has shown that the ^{99}Mo can be extracted from the LEU solution with high efficiency and is in the process of building its production facility. SHINE expects its facility will be able to meet half of the U.S. demand for ^{99}Mo.

NorthStar Medical Radioisotopes uses the ^{100}Mo(γ,n)^{99}Mo production route with an electron linear accelerator (LINAC) to produce the necessary high-energy γ rays. This technology has been demonstrated on a small scale, and commercial-scale testing is in progress. Additionally, NorthStar has partnered with the University of Missouri Research Reactor to irradiate ^{98}Mo targets in a conventional research reactor setting. Both methods produce low-specific-activity ^{99}Mo that requires the use of new generator technology to produce ^{99m}Tc.

All 3 of these companies are in the process of receiving approval to build their radioisotope production facilities. Each of these facilities should be able to meet about half of the U.S. demand for ^{99}Mo, assuming expected normal available capacity is met.

PRODUCTION OF ^{99m}Tc DIRECTLY USING CYCLOTRONS

The direct production of ^{99m}Tc on a biomedical cyclotron was pioneered by Beaver and Hupf in 1971 (*2*), using the ^{100}Mo(p,2n)^{99m}Tc reaction. Over the years, there has been further development on target development and cross-section measurements (*3–5*). However, the inexpensive and plentiful supply of fission-fragment ^{99}Mo provided disincentive for groups to move forward with ^{99m}Tc production on a biomedical cyclotron for wide-scale distribution. The recent global ^{99}Mo supply shortages have renewed an interest in ^{99m}Tc production on biomedical cyclotrons, and recent publications have been assessing the feasibility of cyclotrons producing ^{99m}Tc on a large scale (*6–8*).

Recent work has shown the peak cross section for ^{100}Mo(p,2n)^{99m}Tc to be approximately 15 MeV (*9*), which is within the range of many biomedical cyclotrons being used to produce ^{18}F-FDG. Therefore, a move toward cyclotron-based production of ^{99m}Tc could potentially use an existing network of cyclotrons and would not require investment in new cyclotrons at many sites.

The authors have developed a robust method for target production and handling system for transfer of targets to and from the cyclotron and separation/purification hot cell. High-purity ^{99m}Tc is produced and isolated from the target material, providing ^{99m}Tc that can be used with existing ^{99m}Tc-based radiopharmaceutical kits.

CHALLENGES FOR CYCLOTRON-BASED ^{99m}Tc PRODUCTION

Although the authors have shown the feasibility of ^{99m}Tc production on a biomedical cyclotron, there are many challenges that need to be addressed in order to establish a network of cyclotrons for this production.

Irradiation of the targets ranged from 100 to 240 μA of beam current for durations ranging from 85 min to 6.9 h. These parameters present both technologic and

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logistic challenges. The high level of beam current is not currently feasible for most cyclotrons currently in operation and would require technologic modifications or upgrades. Additionally, many of the cyclotrons are being used for ^{18}F-FDG production from late evening to early morning and will not be available for ^{99m}Tc production because of target availability or beam current constraints. This logistic challenge can be solved if enough ^{99m}Tc can be produced during off hours (i.e., 12 PM to 10 PM) such that even with decay there is sufficient quantity the next morning.

Another challenge is the differing rules between traditional nuclear medicine drugs and PET drugs. For example, most (if not all) of the biomedical cyclotrons used for PET drug production in the United States have their facilities set up in compliance with 21 CFR 212 or USP <823>, which is current good manufacturing practice for PET drugs. Part of the PET drug facility may be set up to comply with USP <797> in order to dispense the bulk PET drugs into prescription doses. ^{99m}Tc is not a PET drug, so the production, separation, and purification of ^{99m}Tc would need to be done in compliance with 21 CFR 210, 21 CFR 211, and USP <797>.

Given both the technologic and the logistic issues and the differing current good manufacturing practice regulations, it is more than likely that separate ^{99m}Tc production facilities will be constructed rather than using existing PET drug production facilities. This, of course, increases the infrastructure costs associated with direct production of ^{99m}Tc on a cyclotron.

Finally, one must take the distribution distance into account. One of the reasons that ^{99m}Tc has gained such a large foothold in nuclear medicine is due to the complementary half-lives of the parent–daughter generator. The 66-h half-life of the ^{99}Mo parent allows for easy, worldwide distribution of generators on a weekly basis. Nuclear medicine clinics do not need to be near the ^{99}Mo producer. Use of cyclotron-based production of ^{99m}Tc will require nuclear medicine clinics to be within a reasonable transportation distance of the production facility because of the 6-h half-life of ^{99m}Tc. Cyclotron-based production of ^{99m}Tc is therefore much more feasible for larger urban locations or areas with strong transportation networks and would present a great challenge for lower-population-density areas of the world.

CONCLUSION

Cyclotron-based production of ^{99m}Tc has been proven feasible and could be part of a solution for a steady, uninterrupted supply of ^{99}Mo/^{99m}Tc. There are significant challenges that must be overcome in order to use a network of cyclotrons for ^{99m}Tc. None of the challenges is insurmountable, but economic factors will play a role.

Regardless of method (B&W, SHINE, NorthStar, direct cyclotron production of ^{99m}Tc), there will need to be significant investment in infrastructure to ensure diversity in providing ^{99}Mo/^{99m}Tc for the greater nuclear medicine community and avoiding the shortages that have affected the nuclear medicine community over the past several years. More than likely it will be a combination of these different methods along with conventional reactor methods that will provide ^{99}Mo/^{99m}Tc for the nuclear medicine community in the decades to come.

DISCLOSURE

No potential conflict of interest relevant to this article was reported.

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