

Radioisotope Therapy and Clinical Trial Design: The Need for Consensus and Innovation

Radioisotope therapy (RIT) is one of the oldest interventions in nuclear medicine. Radioiodine has been used to treat thyrotoxicosis since 1941 (1), and ^{89}Sr was first reported as an effective palliative treatment in patients with painful bone metastases in 1942 (2). Yet despite this long history, RIT has not achieved widespread use in the larger oncologic community, nor, with the exception of radioiodine therapy for thyroid cancer, is it routinely available in most departments of nuclear medicine. Many of the newer therapeutic radiopharmaceuticals have required much time to get to market. Regulatory issues with respect to trial design, dosimetry, and endpoints remain unresolved.

The reasons for this state of affairs are complex; they include (inaccurate) perceptions of expense and complexity, radiopharmaceutical trial design issues, limited phase III and IV clinical trial data, and nuclear medicine departments that are often ill equipped to provide therapeutic rather than diagnostic services.

RIT is typically given as a single intervention, in contradistinction to other forms of radiation therapy; only recently have the benefits of fractionation of low-dose-rate RIT been shown in terms of both palliating symptoms and stabilizing metastatic disease. These preliminary data allow the initiation of clinical trials to evaluate whether multiple fractions are less toxic and more effective than single large administrations. RIT is also usually administered as a monotherapy; increasingly, cancer treatment is administered as combination therapy, and data are now accumulating to show that additional interventions with radiotherapy or chemotherapy can enhance the effectiveness of RIT.

^{89}Sr provides a good example of many of the perceived difficulties of RIT. After an initial rapid expansion of clinical use in the early 1990s, referrals have now contracted in most centers to discouragingly low volumes, although, increasingly, the literature has reported the effectiveness of bone pain palliation with radiopharmaceuticals (3,4). The indications for the use of Metastron (Amersham Health, Princeton, NJ) and Quadramet (Berlex Laboratories Inc., Montville, NJ) in patients with cancer metastatic to bone are

well established and described in the literature (5). Indications for treatment include positive findings on bone scans, a projected survival of 3 mo, a Karnofsky score of ≥ 60 (6), and an adequate blood count. Treatment has also been shown to be effective as an adjunct to external-beam radiotherapy and in delaying the progression of painful metastatic sites (7). Yet in many centers, referrals are made in the last month or two of a patient's life, when Karnofsky scores are low and blood counts are falling. Treatment is often administered at the end of all other standard and experimental therapies. It is little wonder that our oncologic colleagues perceive this therapy as ineffective (8). The centers in which radiopharmaceutical pain palliation is most effective are those where joint clinics with oncologists have been established and where clinical involvement is high (9).

The article by Sciuto et al. (10) in this issue of *The Journal of Nuclear Medicine* makes an important contribution to the nuclear medicine community and to the practice of RIT. The article not only explores the use of adjuvant chemotherapy with RIT but also shows the benefit of a rigorous clinical trial methodology with clearly defined criteria for entry into the protocol and for evaluating response (11–14). The large series of patients builds on data previously reported by this group, exploring the way in which the effectiveness of pain palliation with ^{89}Sr can be enhanced (15,16). The clear benefit shown in the patients receiving adjuvant chemotherapy is a wake-up call to the nuclear medicine community to expand and enhance its expectations about RIT and to apply the same aspirations and expectations to this treatment as are applied to other cancer treatments.

The article (10) is timely in that it confirms the data of Tu et al. (17), who, in a trial comparing ^{89}Sr plus doxorubicin with doxorubicin alone after induction chemotherapy, showed that median survival was 13 mo longer for patients who received ^{89}Sr plus doxorubicin than for patients who received doxorubicin alone. This latter well-designed, appropriately controlled trial showed palliative benefit and an apparent significant survival advantage. It is important to recognize that this group of patients was also pretreated with chemotherapy.

The article by Sciuto et al. (10), taken in conjunction with that by Tu et al. (17), clearly shows that adding chemotherapy for selected patients can significantly enhance the effectiveness of ^{89}Sr . These data are somewhat supported by

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articles describing an improved response to metaiodobenzylguanidine (mIBG) by the use of adjuvant chemotherapy, most frequently cisplatin, that increases the palliative benefit. No clear survival benefit occurred in these patients (18–21). These clinical trials are on relatively few patients, reflecting the weakness of much of the RIT literature. Further work is needed to confirm the effectiveness (22) and clinical benefit of adjuvant therapy.

The article by Sciuto et al. (10) reports that a relatively low dose of cisplatin enhances effectiveness, and although the mechanism of this improved efficacy is not clear, data in the mIBG literature show that cisplatin and doxorubicin enhance *N*-acetyltransferase gene expression (23). An important review of the possible mechanisms of action of bone-seeking radiopharmaceuticals discusses the complex interplay of genetic and local mechanisms in relieving pain (24) and shows many areas of overlap with the in vitro mIBG literature. These discussions may indicate a fruitful area of in vitro work: the evaluation of mechanisms to enhance the effectiveness of low-dose-rate RIT (25).

Sciuto et al. (10), by limiting the question asked of an individual trial, show a channel to the development of RIT clinical trials. ^{89}Sr is clearly palliative therapy in patients with advanced cancer. Therefore, as monotherapy, ^{89}Sr is unlikely to achieve anything beyond palliation; certainly, the literature includes no convincing reports of a survival advantage. The question of whether response improves with adjuvant chemotherapy is unequivocally answered by this trial, making the survival benefit after priming chemotherapy reported by Tu et al. (17) all the more exciting and all the more reason for expanding the role of phase IV trials to the evaluation of the effectiveness of low-dose-rate therapy in combination with adjuvant treatments. These data point to the maturation of RIT as an oncologic intervention, placing a burden not only on the radiopharmaceutical industry but also on the nuclear medicine community. Recent discussions by the Therapy Council of the Society of Nuclear Medicine to establish a framework by which clinical trial methodology can be developed and by which criteria for assessment of outcomes of RIT trials can be established become all the more encouraging. However, this framework does require the development of a cooperative intergroup along the lines of the Radiation Therapy Oncology Group to provide the structure by which these important questions of clinical use can be answered.

The introduction of new therapeutic radiopharmaceuticals is fraught with risk (26). The market for radiopharmaceuticals worldwide is well recognized to be less than that for a single successful drug in the pharmaceutical industry, and in our community, the risk-to-benefit ratio does not favor innovation. The establishment of good clinical trial methodology, specific endpoints for RIT, and innovative uses for adjuvant therapy will go far toward expanding and enhancing the future of this effective treatment. A parallel need is the significant expansion of radiobiology research to fully understand the mechanism by which RIT works. It is only through this understanding that the overall effective-

ness and penetration of this form of treatment can be enhanced to the benefit of all our patients.

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