

# Targeted $\alpha$ -Particle Therapy of Microscopic Disease: Providing a Further Rationale for Clinical Investigation

As is the case with diagnostic nuclear medicine, a major consideration in the development of targeted radiotherapeutics is to seek a balance between conceptual elegance and practicality. Nowhere is this more apparent than in the selection of the nature of the radiation to be exploited and the radionuclide that will be used to deliver this radiation. From a pragmatic perspective, convenient availability and distribution of the radionuclide at a reasonable cost are paramount. The multi-day half-life  $\beta$ -emitters  $^{131}\text{I}$  and  $^{90}\text{Y}$  are notable examples and it is not coincidental that the first 2 Food and

get concentration and radiopharmaceutical delivery on treatment efficacy through cross-fire irradiation.

Ideally, the focus of targeted radiotherapy should be on minimum residual disease settings, where tumor burden is lowest, because these are the applications in which this treatment strategy has the greatest prospect of making a meaningful clinical impact (2). Examples of minimum residual disease include micrometastases and residual tumor margins that remain after surgical debulking as well as neoplasms, such as ovarian carcinoma and neoplastic meningitis, that spread as thin sheets on compartmental surfaces. Treatment of malignancies such as these with routinely available  $\beta$ -emitters would be a daunting task because the range of their radiation is poorly matched with the dimensions of these types of tumors. For example, even if all of a labeled molecule were bound to a 0.2-cm-diameter metastasis, only 1.5% and 17% of the  $\beta$ -energy of  $^{90}\text{Y}$  and  $^{131}\text{I}$  would be deposited in the tumor with the remainder being delivered to neighboring normal tissues (3). Because their range in tissue is only a few cell diameters,  $\alpha$ -particle emitters have emerged as an attractive class of radionuclides for targeted radionuclide therapy, particularly for the treatment of minimal residual disease (1,4). Not only do  $\alpha$ -particles have a considerably shorter tissue path length than  $\beta$ -particles but they also have been shown to be considerably more cytotoxic than  $\beta$ -particles, reflecting their high linear energy transfer nature (5).

Unfortunately, a major impediment to the development of targeted  $\alpha$ -particle therapy is the very limited

availability of radionuclides with characteristics appropriate for clinical use. In addition to poor radionuclide supply, other factors that complicate  $\alpha$ -particle radiotherapy are the need for relevant data relating to normal organ toxicity and more complicated methodologies for calculation of radiation dosimetry (6). From a chemical perspective, the short range and high decay energy of  $\alpha$ -particles can interfere with labeling chemistry, confounding the preparation of therapeutic levels of radiopharmaceutical (7). Therefore, it is important to demonstrate that the potential clinical benefit of  $\alpha$ -particle-emitting targeted radiotherapeutics justifies the additional hurdles associated with their use. However, this is complicated by the fact that evaluating the efficacy of a targeted radiotherapeutic for minimal residual disease, particularly in an orthotopic model, can be a challenging task.

The article by Elgqvist et al. (8) in this issue of *The Journal of Nuclear Medicine* is the latest in a series of excellent papers (9–13) that explore the therapeutic potential of treating animal models of human ovarian cancer with intact and fragmented monoclonal antibodies (mAbs) labeled with the  $\alpha$ -particle-emitting radiohalogen  $^{211}\text{At}$ .  $^{211}\text{At}$  has many attractive characteristics for this and other potential applications of targeted  $\alpha$ -particle radiotherapy that have long been recognized but only recently begun to be exploited for clinical studies (14).  $^{211}\text{At}$  can be readily produced via the  $^{209}\text{Bi}(\alpha, 2n)^{211}\text{At}$  reaction. The impediment to its more widespread use is the scarcity of medium-energy cyclotrons equipped with 25- to 30-MeV  $\alpha$ -particle

See page 1342

Drug Administration–approved targeted radiotherapeutics,  $^{131}\text{I}$ -tositumomab (Bexxar; GlaxoSmithKline) and  $^{90}\text{Y}$ -ibritumomab tiuxetan (Zevalin; Biogen Idec, Inc.), respectively, are labeled with these radionuclides. Clearly, convenience was not the only consideration. The mean range of the  $\beta$ -particles emitted by  $^{131}\text{I}$  and  $^{90}\text{Y}$  in tissue is of the order of 50–200 cell diameters (1), which is advantageous for the treatment of larger tumors. Furthermore, the long  $\beta$ -particle path length can help minimize the deleterious effects of heterogeneities in tumor molecular tar-

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beams, which are required for efficient production. Its 7.2-h half-life is long enough to permit delivery to centers distant from the site of  $^{211}\text{At}$  production (in this case, from Copenhagen to Göteborg, a distance of about 320 km [200 mi]). Furthermore, its half-life is compatible with the pharmacokinetics of a variety of molecular carriers, ranging from small molecules to intact mAbs, with the caveat that locoregional administration, as described by Elgqvist et al. (8), likely will be needed with larger proteins.

In the article, Elgqvist et al. (8) carefully evaluated the therapeutic efficacy of  $^{211}\text{At}$ -labeled MX35 F(ab')<sub>2</sub> against differentially advanced OVCAR-3 ovarian carcinoma growing in the intraperitoneal compartment of athymic mice. MX35 is a murine mAb reactive with a cell-surface glycoprotein expressed homogeneously and at high levels on human epithelial cancers (15), characteristics desirable for use with  $\alpha$ -particles because cross-fire irradiation of antigen-negative tumor cells will not be high. Substitution of MX35 F(ab')<sub>2</sub> for the intact MX35 studied previously (13) would be expected to increase the homogeneity of delivery because of its smaller molecular size and high diffusivity.

A key feature of the article presented in this issue of the *Journal* is the use of scanning electron microscopy (SEM) of sentinel groups of mice to determine the size of tumors at the time of treatment. In this way, it was possible to perform dosimetry calculations that were based on real rather than estimated tumor burden. The effect of tumor size on efficacy was evaluated by varying the time interval between OVCAR-3 tumor inoculation and treatment with a fixed dose of  $^{211}\text{At}$ -labeled mAb from 1 to 7 wk. This experimental design is appealing because it better reflects the circumstances to be encountered in clinical targeted radiotherapy, where tumors with different geometric characteristics are treated with a fixed radioactivity level of radiopharmaceutical. Furthermore, by using an orthotopic tumor model, the investigators were able to refine the analysis of the

tumor-free fraction at the end of the 8-wk study in terms of the presence of macroscopic tumors, microscopic intraperitoneal tumors, as well as ascites. Limitations of murine xenograft models notwithstanding, the ability to stratify response in this way should provide a more meaningful reflection of clinical potential than possible, for example, by measuring the growth delay of subcutaneous xenografts.

Homogeneity of tumor dose deposition is critical to the success of targeted radiotherapy and this is most difficult to achieve with radionuclides such as  $^{211}\text{At}$  that emit radiation of short range (55–70  $\mu\text{m}$ ). In the Elgqvist et al. study (8), SEM demonstrated that the maximum tumor radii in the 5 groups of treated animals were 30, 45, 95, 160, and 340  $\mu\text{m}$ , making it possible to evaluate response in tumors with sizes both above and below the tissue range of  $^{211}\text{At}$   $\alpha$ -particles. For tumors with radii below the range of these  $\alpha$ -particles, the probability of being tumor free was high, and not considerably different for  $^{211}\text{At}$ -labeled MX35 F(ab')<sub>2</sub> (0.94) and  $^{211}\text{At}$ -labeled Rituximab F(ab')<sub>2</sub> control (0.74). This is not unexpected, given that under these conditions the entire tumor could be irradiated efficiently by unbound radioactivity in the peritoneal fluid. As tumor size increased, the probability of being tumor free decreased and a significantly higher tumor response was observed for the  $^{211}\text{At}$ -labeled specific mAb fragment. The later observation is consistent with an increased number of decays occurring on the surface of the tumor, within range of the tumor interior, as a consequence of antigen binding.

A noteworthy goal of the article by Elgqvist et al. (8) is that, instead of limiting analysis of therapeutic outcome to a qualitative discussion, comprehensive dosimetry calculations were performed in an attempt to relate radiation dose to response. In addition to SEM-based tumor size, input data for these calculations included cell and nucleus diameters determined by transmission electron microscopy and counting of radioactivity in peritoneal fluid and other tissues from biodistribu-

tion measurements. A compartmental model developed by this group (13) was then combined with a Monte Carlo-based dosimetry platform (6) to calculate the distribution of mean specific energy per event, from which the mean absorbed dose was derived. Because it was not possible to measure the distribution of radioactivity within the tumors, 2 extremes were assumed: binding of all  $^{211}\text{At}$  to the cell surface and uniform distribution of decays within the tumor.

These calculations demonstrated the critical role tumor size plays in determining treatment efficacy in this type of model. For larger tumors, the dose deposited in different regions of the tumor decreased in interior regions, adversely affecting the tumor-free fraction. Although there was some correlation between mean absorbed dose and response, a more telling parameter was the percentage of cells receiving zero dose, which was about 50% for the largest group of tumors. Nonetheless, the mean absorbed dose calculated for the least favorable set of circumstances—that is, 340- $\mu\text{m}$ -radius tumor with decays confined to the tumor surface—was 22 Gy (vs.  $\sim 540$  Gy for uniformly distributed  $^{211}\text{At}$  and tumors with radii  $\geq 95$   $\mu\text{m}$ ) compared with only 0.3 Gy for bone marrow.

This study provides a rational basis for evaluation of  $^{211}\text{At}$ -labeled MX35 F(ab')<sub>2</sub> for the treatment of patients with ovarian carcinoma; however, a reasonable question would be whether a more readily available radionuclide, such as  $^{90}\text{Y}$  or  $^{131}\text{I}$ , might offer similar benefit. Although not directly addressed by these authors, this question has been evaluated by Bloomer et al. (16), who compared the efficacy of an  $^{211}\text{At}$ -labeled colloid with radiocolloids labeled with  $^{32}\text{P}$ ,  $^{90}\text{Y}$ , and  $^{32}\text{P}$  in a murine ascites tumor model. All radiocolloids prolonged survival to varying degrees but only the  $\alpha$ -emitter was curative. Increasing the administered dose of the  $\beta$ -emitters resulted in unacceptable toxicity, presumably reflecting the irradiation of normal tissues near the peritoneal cavity due to the long  $\beta$ -particle range.

The ability to obtain excellent tumor control without morbidity in the mouse provides a strong rationale for pursuing the development of  $\alpha$ -particle-emitting radiotherapeutics such as  $^{211}\text{At}$ -labeled MX35 F(ab')<sub>2</sub> for use in minimal residual disease settings, despite their greater logistic challenge. Indeed, a phase I trial evaluating the pharmacokinetics and dosimetry of  $^{211}\text{At}$ -labeled MX35 F(ab')<sub>2</sub> has now been initiated in recurrent ovarian cancer patients in good remission after second-line chemotherapy (Jörgen Elgqvist, written communication, April 26, 2006). Hopefully, the results from this clinical trial will provide additional evidence that  $\alpha$ -particle-emitting radionuclides such as  $^{211}\text{At}$  are an essential component of the radiotherapeutic armamentarium and perhaps even provide motivation in the not too distant future for commercial consideration.

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