OBR

Radiopharmaceuticals Need a Jump-STaRT

by Michael D. Becker

Three radiopharmaceuticals have been FDA approved to treat cancer or support cancer therapy. Without the market acceptance of these products by oncologists, further research and development of promising new radiopharmaceutical therapies could be compromised.

Radiation has been an effective tool in the war against cancer for more than a century. The original and still predominant mode of administration is via external methods wherein a radiation source is directed at the intended target or region. Unfortunately, this "outside in" approach has the drawback of causing collateral damage to healthy organs and tissues that lie on either the path between the source and the target or beyond the intended target on the "exit" pathway. While newer techniques, such as intensity-modulated radiation therapy (IMRT), can help reduce radiation exposure to normal tissues; limitations still exist. Precise knowledge of disease extent and location is required for effective targeting; yet small volume disease often cannot be identified using traditional imaging techniques.

Beginning in the late 1990s, intravenous delivery of radionuclides paired with tumor targeting carriers emerged. Called systemic targeted radionuclide therapy (STaRT), this approach offers the promise of selectively targeting disease sites while sparing normal tissue. Particle emitting radionuclides biologically targeted to disease sites deliver high radiation doses over very short ranges in an "inside out" manner. Because the range of these particles is limited (typically several millimeters at the maximum) radiation exposure to surrounding normal organs and tissues is limited. The major challenges in developing such agents involve achieving highly-specific targeting and ensuring that the physical properties—such as the rate of decay—of the therapeutic radionuclide are appropriately paired with the biologic characteristics of the targeting agent. One of the first such agents, Quadramet® (samarium Sm-153 lexidronam injection), was introduced commercially in 1997 by Cytogen Corporation for the relief of pain arising from metastatic bone disease. The product consists of a small molecule (ethylene diamine tetra methylene phosphonate, or EDTMP) that when combined with samarium-153, a therapeutic isotope with favorable physical characteristics, targets metabolic activity associated with cancer progression to the skeleton.

Quadramet®

In 2003, the U.S. Food and Drug Administration (FDA) approved two radioactive labeled monoclonal antibodies for the treatment of follicular non-Hodgkin's lymphoma (NHL). Both products utilize monoclonal antibodies that target an antigen expressed by certain normal and malignant

B-cell lymphocytes. Zevalin® [ibritumomab tiuxetan; Biogen Idec] employs yttrium-90 as its therapeutic payload, while Bexxar® [tositumomab; GlaxoSmithKline] uses iodine-131. Zevalin and Bexxar are both effective treatments for patients with relapsed or refractory NHL.

A recent article in the *New York Times* ("2 Lymphoma Drugs Go Unused, and Backers Cite Market Forces," by Alex Berenson, July 14, 2007) reports that despite the established efficacy and tolerability inherent in directly targeting tumor sites with radiolabeled compounds, fewer than 10% of patients who are candidates for Zevalin, Bexxar, or Quadramet ever receive them. The low level of market penetration for these products is due to a variety of factors, including:

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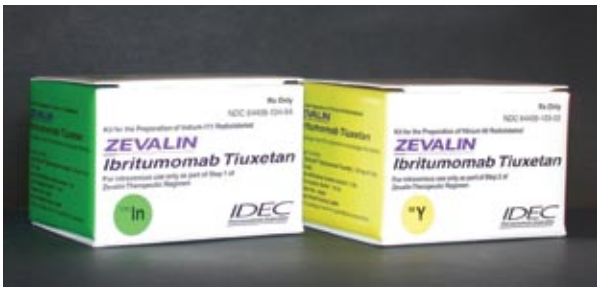
- **Control:** While medical oncologists are the key prescribing audience for STaRT therapies, most aren't licensed to administer radiopharmaceuticals—resulting in referrals to radiation oncologists and/or nuclear medicine physicians.
- **Combinability:** There has been a paucity of clinical data demonstrating the benefits and tolerability of radiopharmaceuticals when used in combination with contemporary oncology treatments with potentially overlapping toxicity profiles.
- **Safety:** Early forms of radiotherapy were associated with side effects, such as myelosuppression, causing medical oncologists to reserve such treatments for late-stage cancer patients.
- **Economics:** Lack of financial incentive is also a culprit, as most oncologists are not paid to administer radiopharmaceuticals. Berenson cited two cases where patients were given these treatments only after demanding them. He points out that because radiopharmaceuticals must be administered in a hospital, not private practice offices, doctors cannot be reimbursed for them, unlike office-administered treatments such as chemotherapy.

Bexxar®



Zevalin®

It is often darkest before the dawn, however, and there are reasons for optimism for the field of STaRT therapy going forward. For example, at the 2007 American Society of Clinical Oncology (ASCO) annual meeting GlaxoSmithKline reported long-term efficacy data from a Phase 2 trial of a single one-week course of frontline treatment with Bexxar in 76 patients with newly-diagnosed advanced follicular NHL. Patients achieved estimated 8-year and 10-year overall survival rates of 86%. Additionally, 50% of patients survived without progression of disease at 8 years following therapy. For patients who achieved complete remission, the median time before their disease progressed was 9.2 years. An overall response rate and complete remission rate of 95% and 75%, respectively, were observed.

Bexxar is also currently being evaluated in a Phase 3 Southwest Oncology Group (SWOG) study evaluating cyclophosphamide, hydroxydoxorubicin, vincristine, and prednisone (CHOP) chemotherapy in cont. on pg 14 >>

combination with Rituxan® [rituximab; Genentech, Biogen Idec] versus CHOP in combination with Bexxar in patients with newly-diagnosed follicular NHL. Results are expected in 2009 and, if favorable, Bexxar could supplant Rituxan's established and lucrative role in the upfront NHL setting. This could create a fundamental shift in oncologists' use of radiopharmaceuticals as a drug class.

With bone pain representing a significant quality-of-life concern for patients with metastatic prostate cancer, studies are underway to evaluate the safety and feasibility of repetitive co-administration of Quadramet, with docetaxel, an FDA-approved chemotherapy drug to treat late-stage prostate cancer. Since the main side effect of both Quadramet and chemotherapy is myelosuppression, such studies were needed to dispel concerns about potentially overlapping toxicities that could limit or delay subsequent treatment options—one of the main historical barriers to the use of Quadramet. Clinical data presented at the 2007 ASCO demonstrated that repeated doses of Quadramet with docetaxel are safe and do not appear to impair the effective delivery of docetaxel in most patients. Both drugs were administered at their respective, FDA-approved therapeutic doses without compromising patient safety. It remains to be seen if the availability of this new combinability data will foster increased acceptance of Quadramet, or whether the lack of economic incentives for medical oncologists will stifle such progress.

Not only is it potentially safe to administer radiopharmaceuticals in combination with contemporary therapeutic agents, such practice may actually be beneficial from an efficacy perspective. For example, at the XIth International Myeloma Workshop, researchers reported results suggesting that it is possible to capitalize on the radiosensitizing properties of contemporary oncology agents to enhance the benefits of STaRT therapy. Cytogen reported Phase 1 data showing the promising anti-tumor activity and safety profile of a novel combination regimen of Quadramet with the protease inhibitor, bortezomib, for the treatment of multiple myeloma. Results from the study demonstrated that the combination was tolerable and of 32 evaluable patients, 15 participants, or more than 46% achieved a response or stabilization of their disease. Of these, 6 patients responded to the combination regimen, with 3 achieving a complete response (CR) and 3 achieving a minor response (MR). Importantly, of the 15 patients who achieved either a response to treatment or stabilization of their disease, 9 had previously failed treatment with bortezomib.

Finally, there are times when the main side effect of STaRT therapy, namely mild and transient bone marrow suppression, may actually be beneficial. Hematological malignancies are known to be highly susceptible to radiation treatment. Total-body irradiation was once a part of conditioning regimens prior to bone marrow transplants; however, the toxicities resulting from the use of "outside in" irradiation more than offset the incremental efficacy associated with the treatment. Current conditioning regimens involve treating diseased bone marrow with high-dose chemotherapy followed by a transplant with previously harvested stem cells or those from a closely matched donor. However, even when patients have a good initial response to a bone marrow stem-cell transplant, the disease often relapses because the chemotherapeutic conditioning regimen prior to the transplant fails to kill a sufficient percentage of the cancer cells.

Data reported at this year's ASCO demonstrated that adding Bexxar to chemotherapy as a conditioning regimen prior to autologous stem-cell transplant in patients with relapsed or high-risk chemosensitive diffuse

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large B-cell lymphoma, resulted in 78% of the patients achieving a complete remission following the transplant. Three year progression-free survival and overall survival were 70% and 81%, respectively. These results compare favorably with previous studies of chemotherapy alone followed by autologous stem-cell transplant and compared with a similar cohort receiving chemotherapy alone, no increased toxicity could be detected.

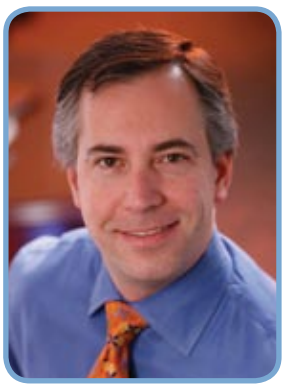
Further, Phase 1 and 2 trials conducted at the Mayo Clinic combining high-dose Quadramet (approximately 30 times the approved dosage for pain palliation) to melphalan chemotherapy as a conditioning regimen prior to autologous stem-cell transplant in patients with multiple myeloma demonstrated favorable results. About half the patients exhibited complete or near-complete responses—total or near-total absence of the telltale M protein—a marker for the presence of residual myeloma cells in their blood and urine—100 days after the transplant. The results are encouraging and justify further studies to look at duration of response.

. . . the market for therapeutic radiopharmaceuticals could reach $6 billion in 2020 . . .

The business research and consulting firm Frost & Sullivan forecasts that the market for therapeutic radiopharmaceuticals could reach $6 billion in 2020, compared to an estimated $48 million in 1996 and that nuclear medicine will expand into other therapeutic areas as more than 35 clinical trials throughout the United States are researching the potential of such products. These trials are investigating the use of a large number of isotopes in treating several diseases and are being driven mainly by smaller companies.

In conclusion, the emergence of STaRT therapies, including Quadramet, Zevalin and Bexxar, has clearly benefited patients, specifically those with systemic disease. In order to help patients continue to gain access to these important and proven therapies, clinical barriers related to control, combinability, safety and economic incentives must be addressed. Berenson notes in the New York Times that in October 2006 Biogen Idec said it would "evaluate strategic options" for Zevalin, including divesting the treatment. Although Biogen Idec still manufactures Zevalin, it no longer actively promotes it. Additionally, Cytogen recently reduced its research and development guidance for 2007, citing that its focus for the remainder of the year will be on the publication and presentation of ongoing and completed studies while assessing the commercial impact of this information prior to the initiation of new clinical studies involving radiopharmaceuticals.

Hopefully this will be a wake up call to oncologists. Physicians will need to either embrace radiopharmaceuticals or risk the industry abandoning further research and development of these new promising therapies. Patients with cancer, and the doctors who treat them, should have as many tools available to them as possible. Radiopharmaceuticals belong in the tool box. MDB



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