Innovations in Breast Cancer Drug Delivery

by Donald Jewler

Facility development, marketshare, staff, and revenue are all important for the success of *any* breast care center. Beyond these tangible assets (and equally important), however, are the technology and treatments at the heart of the care you provide.

More than 370 new drugs are in development for diseases that disproportionately affect women. Of these, 71 are new anticancer products, including 41 for breast cancer.[1] Innovative cancer therapies are based on current concepts of molecular biology of cancer. These include antiangiogenic agents, immunotherapy, bacterial agents, viral oncolysis, targeting of cyclic-dependent kinases and tyrosine kinase receptors, antisense approaches, gene therapy, and combination of various methods.

One new drug for metastatic breast cancer is designed to bind to and inhibit vascular endothelial growth factor (VEGF), a protein that plays a critical role in the formation of new blood vessels that feed the tumor.[1] Another is designed to encapsulate the drug within microscopic lipid spheres to evade detection by the immune system and resulting in the product circulating in the blood for a longer period of time. The longer circulation allows for longer periods between doses.

Indeed, many new drugs use innovative methods to deliver therapeutic material to a tumor. Novel delivery systems are being developed to supplement conventional chemotherapy and radiotherapy and prevent damage to normal tissues and drug resistance. New methods of delivery are improving both the efficacy and safety of conventional cancer drugs.

A variety of innovative methods of drug delivery are under investigation in breast cancer. These include, but are not limited to, use of:

- *Microparticles—and smaller still, nanoparticles—as carriers of anticancer agents*. These may be injected into the arterial circulation and guided to the tumor by magnetic field for targeted drug delivery.
- *Liposomes, microscopic lipid spheres*. Encapsulating anticancer drugs in liposomes enables targeted drug delivery to tumor tissues and prevents damage to the normal surrounding tissues. Newer liposomes are able to evade recognition by the immune system because of a polyethylene glycol (PEG) coating.
- *Targeted therapies, including monoclonal antibodies*. Monoclonal antibodies are used for the delivery of anticancer payloads such as radionucleotides, toxins, and chemotherapeutic agents to the tumors.

Drug delivery strategies vary according to the type and location of cancer.

A NOVEL NANOPARTICLE ALBUMIN-BOUND TAXANE

Taxanes are used to treat a wide variety of tumor types, including metastatic breast cancer. Because taxanes are not easily soluble, IV administration of current taxanes requires the use of solvents: Cremophor® EL (CrEL), which is a derivative of castor oil, for paclitaxel; Tween® 80 or polysorbate for docetaxel. Both CrEL and Tween 80 are chemically active compounds, and their use has been implicated in clinically important adverse events, including acute hypersensitivity reactions (despite intensive steroid premedication) and neurotoxicity.[2,3] Furthermore, paclitaxel and docetaxel can become entrapped within solvent particles (micelles), resulting in reduced distribution of drug into the tumor tissues.[4]

At the 2003 San Antonio Breast Cancer Symposium, Phase III data were presented for nanoparticle albumin-bound (*nab*) paclitaxel (ABI-007), a unique, next generation, solvent-free albumin nanoparticle taxane in the treatment of patients with metastatic breast cancer. *nab* paclitaxel roughly doubled patient response rates and achieved longer tumor time-to-progression without increasing toxicity, when compared with the standard paclitaxel formulation, Taxol.[2,3]

nab paclitaxel, known as Abraxane™, is a unique Cremophor-free nanoparticle albumin-bound paclitaxel. The albumin nanoparticle paclitaxel complex is about 130 nanometers in diameter. (One nanometer is just one billionth of a meter—half the size of human DNA.)

Formulating paclitaxel with albumin seems to help it get into tumors. How? It is believed that albumin-bound paclitaxel binds to albumin receptors (gp60 or albondin) of endothelial cells within the tumor vasculature.[2] Albumin binding to gp60 receptors triggers the formulation of little "caves," or caveolae, allowing the drug-albumin complex to move across the endothelial cell layer into the tumor tissue.

nab paclitaxel allows for higher doses of paclitaxel (Abraxane 260 mg/m^2 vs Taxol 175 mg/m^2 given every three weeks) to be administered, with almost double the response rates, significantly longer time to tumor progression, and significantly less neutropenia compared with the Taxol, despite the 50 percent higher dose of paclitaxel administered with Abraxane.[3]

Although grade 3 neuropathy has been seen in a significantly higher number of patients treated with Abraxane, resolution of neuropathy occurred much

faster with Abraxane (22 days) than with solvent-based Taxol (79 days).[3]

Abraxane was administered without standard steroid premedication over a 30-minute infusion time, and no hypersensitivity reactions were reported. Still, overall survival data with *nab* paclitaxel have yet to be determined.[2]

OF LIPOSOMES AND IMMUNOLIPOSOMES

Lipid-based drug delivery has been in use since the 1970s. Today, liposomes can be engineered to stably encapsulate doxorubicin, for example, recirculate for periods of several days after IV injection without releasing the drug, penetrate the tumor tissues, and release the encapsulated drug within the tumor.[5]

The size of the liposome affects its ability to deliver encapsulated drugs to disease sites. When the liposomes are too large (larger than the diameter of the gaps in the endothelial wall, which have been shown to be less than 400 nanometers), liposomes do not reach their target destination. Conversely, if the liposomes are too small, the amount of drug delivered to the tumor will be inadequate. The number and composition of lipid layers, the size and charge of the liposomes, and the composition of the internal aqueous space in the liposomes can be altered to enable the efficient and stable incorporation of a wide variety of therapeutic and diagnostic agents.[5]

Recent advances in liposome technology have led to the development of small liposomes coated with polyethylene glycol (PEG). The PEG coating is designed to minimize cell-liposome interactions, allowing liposomes to evade detection by the immune system and resulting in the product circulating in the blood for a longer period of time. The longer circulation allows for longer periods between doses.

Pegylated liposomal doxorubicin hydrochloride for injection (Caelyx®) has been approved in Canada for metastatic breast cancer patients who are at increased cardiac risk. Results of a randomized Phase III clinical study demonstrated that Caelyx had similar efficacy to conventional doxorubicin, while reducing the incidence of several side effects, including alopecia, nausea, vomiting, and cardiotoxicity.[6] However, overall survival based on 286 deaths out of 509 patients (56 percent) was similar in both study arms.

The overall risk for developing a cardiac event was significantly reduced in patients treated with Caelyx, while adverse events related to the skin or mucosa were more prevalent with Caelyx treatment.[6]

Breast cancer is the third indication for Caelyx, which is currently marketed in Canada for the treatment of advanced ovarian cancer in women who have failed first-line, platinum-based therapy, and for the treatment of AIDS-related Kaposi's sarcoma.

Much farther down the pipeline are "immunoliposomes." Doxorubicin has been enclosed in a liposome that includes antibody fragments at the surface directed at the HER-2 growth factor receptor. HER-2 is found on about 30 percent of the more aggressive breast cancers, and the use of an antibody makes it an "immunoliposome." The strategy of immunoliposome delivery may have broad utility for targeted delivery of other anticancer agents.[7]

TARGETED THERAPIES

Targeted agents are compounds that are designed to hit either a single pathway or, in some cases, multiple pathways that control a cancer cell's ability to grow and escape conventional therapy. Targeted therapies allow more precision and fewer side effects than conventional cytoxic drugs.[8]

Chemically coupling antibodies to toxins or radionuclides is the most widely investigated means for increasing their antitumor activity. Two anti-CD20 radioimmunoconjugates, Bexxar® (tositumomab; ^{131}iodine) and Zevalin® (ibritumomab tiuxetan; ^{90}yttrium), were recently approved by the Food and Drug Administration. Targeting tumor neovasculature and angiogenic growth factors and receptors are promising alternative and potentially complementary strategies to direct tumor targeting. An anti-VEGF antibody, bevacizumab (Avastin™), was recently FDA-approved for first-line treatment of patients with metastatic colorectal cancer. Phase III trials are underway to access bevacizumab's effects in patients with metastatic breast cancer.[1]

Several trials are combining targeted therapies for breast cancer.[1] One Phase II trial of 120 patients is examining a Herceptin®-Iressa® combination for women with HER2-positive breast cancer.[8] Herceptin (trastuzumab) is a monoclonal antibody that was the first targeted therapy to be FDA approved, and Iressa (gefitinib) is targeted at the epidermal growth factor receptor, or EGFR, a protein involved in stimulating cancer cell growth. Iressa was the third targeted agent to receive FDA approval. In May 2003, it was approved as third-line therapy for patients who had received chemotherapy for advanced lung cancer. The challenge will be to prove that both drugs in a combination contribute to a favorable result.[8]

Donald Jewler is director of communications at the Association of Community Cancer Centers.

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