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An Overview Of New Modalities And Expected Advances

This article presents an overview of some of the new cancer treatment and diagnostic technologies that already are, or are likely to become, an important part of cancer care in the 1990s.

According to the Pharmaceutical Manufacturers Association (PMA), there are currently 126 cancer medicines in development by 56 different companies. And, because many of the agents are being tested for more than one type of cancer, a total of 225 separate research projects are under way. The PMA estimates that American Pharmaceutical Companies will invest $9.2 billion in research and development (R&D) this year. Moreover, the industry's R&D expenditures have doubled every five years since 1970.

Those R&D figures are not surprising when it is estimated that only 5 out of 4,000 compounds screened in preclinical testing make it to human clinical trials, and only 1 of those 5 agents is approved by the Food & Drug Administration (FDA).

But pharmaceutical and biological agents are, of course, only one of the forms of cancer treatment that are being developed. Significant R&D and product development is also occurring in the areas of radiation and surgical oncology, including photodynamic therapy, hyperthermia, high-dose brachytherapy, sophisticated surgical lasers, and so forth. As Ed Kenney, Senior Director of Proprietary Drugs at Cetus Corporation, so aptly says, we're in an era of "star wars medicine."

This article will provide a glimpse of some of these "star wars" treatments, many of which are likely to be on the market and in use in community-based cancer centers by the end of this decade.

Growth Factors

Earlier this year, FDA approval of the first colony stimulating factors (GM-CSF and G-CSF) cleared the way for the treatment of patients with higher chemotherapy doses, reduced hospitalizations for neutropenia, and decreased hospital stays for bone marrow transplant patients. James Armitage, M.D., Chairman, Department of Medicine, University of Nebraska Medical Center, Omaha, says GM-CSF studies show that, "on average, patients can be discharged a week earlier" following high-dose chemotherapy and autologous bone-marrow transplantation (HDC/ABMT). That, he says, translates into "about a $3,000 per day savings and a cost-reduction potential for this curative therapy of about $20,000." He predicts that with the advent of growth factors that can reduce the risk of ABMTs, more patients will be eligible for the treatment. That, he says, "is the only way to impact the absolute number of cured patients."

Immunex Corporation, Seattle, WA, whose GM-CSF product was approved by the FDA this past March, has a number of more advanced growth products under development, according to Steven Gillis, Ph.D., President, Research & Development. "All of the things that we're doing are aimed at increasing the body's ability to rebound from chemotherapy and radiation therapy treatments." A major focus of the company, Gillis says, "is to see if we can use growth factor products to make bone marrow recover more quickly and [subsequently] be able to increase the frequency or dosage of chemotherapy or radiation therapy." Currently, Immunex has five growth factors in pre-clinical or clinical testing. They are "broader acting and earlier acting agents," Gillis says.

For instance, Interleukin-3 (IL-3) stimulates the production of the white blood cells that generate platelets and the cells that give rise, eventually, to red blood cells. Interleukin-1 Alpha, which is in "phase I trials as both a single agent and in combination with GM-CSF, acts even earlier than IL-3," Gillis says. That is, it affects "very immature white blood cells." Pixie 321 is "an exciting, novel development in that it's a genetically engineered product," he says. "It's a combination protein with elements of GM-CSF and IL-3. In a trial that will begin this year, we hope to raise the levels of infection-fighting granulocytes, macrophages, and platelets with this product."

And finally, Gillis says the company is developing MGF (Steel Factor), "a molecule that we discovered in 1990. It acts on the earliest of all hematopoietic cells, the stem cell, from which all other bone marrow cells develop, and it is vigorous in combination with later-acting growth factors," Gillis explains. Hopefully," he says, "we are designing clinical studies that will show how physicians can use these products in combination."

Gillis believes that growth factors will "change the way we give cancer therapy." He predicts that "more therapy will be given on an outpatient basis, because we will have eliminated the risk of infection and marrow damage." He foresees a future in which "bone marrow transplants are done on an outpatient basis, because we've eliminated the morbidity associated with the procedure." Nevertheless, he admits that a key question has yet to be answered: "Will these products result in dramatic improvements in survival, or only affect the quality of patients' lives?" Personally, Gillis believes they will improve survival, especially, he says, "when they are used in conjunction with high-dose chemotherapy or high-dose radiation therapy."

Genetic Engineering

Cetus Corporation developed and provided to the National Cancer Institute (NCI) the retroviral vector used to program lymphocytes to produce tumor necrosis factor. "Much of the work with IL-2 has involved adoptive immunotherapy," Kenney says. The research by Steve Rosenberg, M.D., of NCI, entails "the harvesting of white blood cells, their manipulation and their reinfusion. White blood cells are removed, incubated for a period of time in IL-2 and reinfused in the patient. Rosenberg has also been studying tumor-infiltrating lymphocytes (TIL). Basically, this research involves removing part of a patient's tumor, which is then placed in IL-2. The lymphocytes that have invaded the tumor are allowed to expand in the IL-2. What Rosenberg has discovered is that when they are reinfused in the patient, they tend to be tumor-specific," Kenney explains. "With the use of retroviral vector, the lymphocytes are programmed to produce tumor necrosis factor when they get back to the tumor." To date, this early work with TIL, IL-2, and TNF has focused on high-mor-

bidity cancers, specifically metastatic renal cell carcinoma and malignant melanoma.

Despite a lot of progress in cancer therapy over the past 30 years, Ed Kenney of Cetus Corporation points out that "we still have a million people diagnosed with cancer every year and one-half million who die from cancer. Clearly, we have a tremendous distance to go." Nevertheless, Kenney is excited about the new cancer therapy products under development, which he believes "will prove effective for tumors that heretofore were untouchable. A classic example," he says, "is metastatic renal cell carcinoma." Currently, according to Kenney, "less than 1 percent of the patients with metastatic renal cell carcinoma survive." Moreover, 20 percent of the patients who contract renal cell carcinoma will develop metastases. Cetus' clinical trials of Interleukin-2 have resulted in responses in the "20 to 40 percent range" for metatastatic renal cell carcinoma, Kenney says. In fact, there is an NCI-sponsored tumor bank at UCLA Medical Center. Patients who contract, for instance, renal cell carcinoma, can have their tumor "banked" at UCLA and if they later develop metastases, such genetically engineered treatments can then be employed.

However, there are severe toxicity problems in developing these genetically-manipulated treatments. According to Kenney, two of Cetus' products—specifically a tumor necrosis factor and an immunotoxin—that are likely to be useful in the treatment of cancer have stalled in the pre-clinical stage of testing because of "difficulties with toxicity." Nevertheless, Kenney believes that solutions to such problems will be found and that such treatments will be successfully brought to market. "Biotechnology companies have powerful tools at their disposal and rapidly developing research techniques," Kenney points out. "And one advantage that biotechnology companies have is that they tend to be engaged in more focused research [than] chemical-based companies, which screen tens of thousands of chemicals."

Liposomes

The severe side effects of doxorubicin, which is prescribed more than any other anti-cancer agent, as well as other chemotherapy agents, may be eliminated, clearing the way for higher patient dosages thanks to the use of liposomes. Phase I and phase II trials of liposome-encapsulated doxorubucin (TLC D-99) by the Liposome Company have demonstrated "significantly less gastrointestinal toxicity and no mucositis" in patients with relapsed breast cancer, according to Marc J. Ostro, Ph.D., Vice Chairman and Chief Scientific Officer for the company. "We don't know the effect on cardiotoxicity yet," Ostro explains, because the effect is cumulative and the number of patients in the phase II trial are too small" to tell. However, "in preclinical testing, TLC D-99 totally eliminated cardiotoxicity in dogs," says Ostro.

Ostro is also confident that "the efficacy of TLC D-99 will prove equal to, if not better than, free doxorubicin in the treatment of relapsed breast cancer, due to the ability to deliver higher dosages." If this new method of drug delivery proves effective, it could be applicable to a number of other anti-cancer agents. Ostro says the company plans to begin trials with another agent in the "not too distant future. We're considering a variety of other agents, such as vincristine, methotrexate, fluourouracil,

etc. I think the process has the potential for reducing the toxicity of many drugs."

The Liposome company also recently made a technical breakthrough that may revolutionize the ability to detect liver metastases in CT scans. "In the past, there have been a lot of problems with attempts to develop particulate imaging agents for CT scans," Ostro explains. "With particulates, such as fluorocarbins, there was a problem with toxicity." And, "attempts to use liposomes were stymied when researchers couldn't find a way to increase the level of iodine that they could carry to the liver," says Ostro. But the company has now developed an entirely "new type of liposome that has allowed us to encapsulate as much as 6 milligrams of iodine to 1 milligram of lipid versus 1 milligram of iodine to 1 milligram of lipid," Ostro says. As a result, "it is allowing us, for the first time, to give doses of lipid-encapsulated contrast agent in a high enough quantity to achieve sharp contrast of the liver." In fact, Ostro says, the new technique has produced "incredible clarity in CT scans of dogs."

Antineoplastic Agents

Bristol-Myers Squibb has a number of new antineoplastic agents under development. Those agents range from "variants of existing cytotoxic agents to completely new molecules," says Karl Erik Hellstrom, M.D., Ph.D., Vice President & Head, Oncology Drug Discovery. And although Bristol-Myers Squibb is also conducting biological research (oncogenes, suppressor cells, growth factors, and so forth), Hellstrom maintains that "cytotoxic agents will continue to be a mainstay of cancer therapy for a number of years to come."

The company has already discovered variants of such drugs as etoposide, cisplatin, mitomycin, and carboplatin, which have "certain therapeutic advantages over those existing agents," Hellstrom explains. "Hopefully," he says, "these relatives of existing agents will be in clinical use within the next few years." In addition, the company is devoting considerable resources to "producing sufficient amounts of the drug taxol," Hellstrom notes. He believes that taxol, which has "shown a great deal of promise in the treatment of refractory ovarian cancer, as well as breast and even lung cancer," will be the next novel anticancer drug on the market.

Bristol-Myers Squibb is "continuing to discover new antineoplastics," but because it's "drug discovery program is relatively new," Hellstrom says, they are "just beginning to see the fruits" of such research. Nevertheless, he says that four new molecules in early clinical testing show great promise against cancer.

Finally, the company is conducting "early exploratory research into the mechanisms and actions of oncogenes and suppressors," Hellstrom says. And, in the area of biologicals, it has an "intense program exploring the use of monocional antibodies for delivering anti-cancer agents." The antibody L-6, combined with a radioactive isotope, which has already been tested on about 50 patients at the University of California, Davis, has achieved "partial remissions in patients with advanced disease," Hellstrom says. And the company plans to embark on "more extensive studies of L-6 and its ability to localize tumors," in conjunction with Memorial Sloan Kettering Cancer Center. This study, according to Hellstrom, will examine the antibody's drug delivery capabilities. In addition, the antibody, BR-96, has been conjugated with doxorubicin and has shown "remarkably good results in mice studies for breast, colon, lung, and ovarian tumors," Hellstrom notes.

By the end of this decade, Hellstrom predicts, "studies at the genetic level of cancer" will be active. Such studies, he believes, will "ultimately make it possible to find molecules that demonstrate a greater selectively in inhibiting cancer cells." Such research will enable us to "learn more about the various diseases that we group under cancer, and the process of neoplastic transformation."

Radiation Oncology

Some of the high-cost therapies, such as proton and neutron therapy, and the use of charged particles, which have limited applications, are likely to be replaced by equally effective but much less expensive therapies, predicts Kenneth Wheeler, Ph.D., Director of Experimental Radiation Oncology, Bowman Gray School of Medicine, Wake Forest University, Winston-Salem, NC. New innovations such as gamma knives, combined high-dose brachytherapy and hyperthermia, and the development of predictive assays of tumor responses to radiation therapy are rapidly emerging.

Clinicians at Bowman Gray are now using gamma knives to treat metastatic brain tumors. "Gamma knives are attached to linear accelerators and used to place an intense beam of radiation in areas as small as one millimeter," Wheeler explains. Bowman Gray is one of four test units for the new therapy in the United States.

Another area that is up and coming is the "combination of heat and brachytherapy. Tumors are implanted with the isotope palladium, which can be done on an outpatient basis, and the seeds are then heated by microwave application," Wheeler says. It is the simultaneous application of heat and radiation that, in the past, could not be accomplished. Moreover, because the "dose is well-defined from the implants, the interaction of hyperthermia and tissue is minimized," Wheeler notes. Moreover, the defined dose enables clinicians to use this form of combination therapy in patients who have already been irradiated. Recently NCI approved a protocol using the combination therapy in the treatment of head and neck tumors.

Moreover, Wheeler believes that some combination of two new techniques that are currently being studied may lead to a "predictive assay" that will enable clinicians to determine which head and neck tumors will not be responsive to standard therapy and to modify treatment of those tumors either prior to or during the early stages of treatment. Such predictive assays hold a "great deal of promise in boosting the curability of head and neck tumors," Wheeler says.

"The development of new techniques and the physics associated with these techniques suggest that new technologies, such as the gamma knife, may be a feasible replacement to proton therapy. There are other ways to achieve the same results," he says—techniques that are much less costly. For instance, a gamma knife costs approximately one-half million dollars, compared to the multimillion dollar cyclotron.

Summary

It is clear that major new discoveries in the areas of biologicals, antineoplastics, detection, radiation therapy, and so forth are rapidly advancing. Scientists are unlocking the secrets of the cancer cell at the molecular level, and at a remarkable pace. New innovations hold great promise of increasing the dose intensity of chemotherapy and radiation therapy while decreasing the side effects of those treatments. Hopefully, as Gillis notes, these advances will not only improve the quality of life for cancer patients, but improve survival. ■