TARGETED THERAPY FOR CANCER IN yesterday’s terms included such items as 5-flouracil (5-FU), which targets thymidylate synthase in many cancers, and tamoxifen for estrogen receptor positive breast cancer. These agents, even though they are toxic agents, do have targets.

The aim of current research is to find therapies that selectively destroy cancer cells, and leave normal cells alone, while producing less toxicity than traditional chemotherapy agents. Traditional chemotherapy agents do kill cancer cells but they also typically kill other cells such as those of the gastrointestinal tract and hair follicles. These new selective killing agents are referred to as targeted therapies.

In today’s terms, targeted therapies for cancer are agents that target one of the six hallmarks of cancer. These hallmarks are what drive cancer growth: self-sufficiency in growth signals, insensitivity of antigrowth signals, limitless replicative potential, evading cell death (or apoptosis), sustained tumor blood vessel formation, and tumor invasion and metastasis. Each one of these hallmark represents an area where an oncology drug has been designed. Some of the specific targets in each area are shown in Exhibit 1. An additional area besides the six hallmarks that is being targeted is the immune system. There are FDA-approved medications targeting tumor angiogenesis, growth signal transduction, and cell cycle apoptosis, in addition to others. Many different agents are also in various stages of clinical development.

The various ways to deliver one of these agents to cancer cells are outlined in Exhibit 2. For example, ibritumomab (Zevalin®) and tositumomab (BEXXAR®) deliver radioisotopes to lymphoma cells. Rituximab (Rituxan®) and alemtuzumab (Campath®) are monoclonal antibodies that induce cell lysis by activation of the host’s immune system. Bevacizumab (Avastin®), cetuximab (Erbitux®), and trastuzumab (Herceptin®) are other monoclonal antibodies that bind to the extracellular domains of receptors involved in cell growth. Gemtuzumab (Mylotarg®), a combination monoclonal antibody and cytotoxic molecule, is used to deliver the cytotoxic molecule in acute myelogenous leukemia (AML). Bortezomib (Velcade®), gefitinib (Iressa®), imatinib (Gleevec®), sunitinib (Sutent®) are all small molecule drugs which target specific proteins within cancer cells and stop the cancer cells from growing. Ribozymes block protein synthesis.

The target therapies that have been approved for use in the U.S. thus far are not without adverse effects. For example, agents which target the epidermal growth factor receptor such as cetuximab, panitumumab (Vectibix®), gefitinib (Iressa®), imatinib (Gleevec®), sunitinib (Sutent®) cause rash in a large percentage of recipients. The agents that target vascular endothelial growth factor (VEGF) or vascular endothelial growth factor receptor (VEGFR inhibitors) in various
tumors include bevacizumab, sunitinib, imatinib, and sorafenib (Nexavar®). Because these agents target the vascular system, the adverse effects include hypertension and, rarely, heart attack and heart failure.

For several cancers, studies of these targeted agents are showing an increase in overall survival. For example, in head and neck cancer, adding cetuximab with radiation or with cisplatin and radiation gives a significant survival benefit of about 10 months improvement in median overall survival. Historically with gastrointestinal stromal tumor (GIST), people would live about 20 months. With imatinib, treated median overall survival is 70 months, which is a revolutionary improvement.

Differences in response to these various targeted agents can be seen across different patient populations. For example, erlotinib has the most activity in females, non-smokers, and younger patients. Getifinib, while not providing a survival difference in lung cancer in the U.S., produces a 20 percent response rate in Asian countries. Although FDA approved, studies with getifinib have shown very little difference in survival. Canada and Europe both denied approval of this agent, but the FDA approved the drug largely based upon the one-year survival differences of about 7 percent in pancreatic carcinoma.

Many of these targeted therapies are producing significant complete responses, which means that cancer growth cannot be detected by current methods. Complete responses do not necessarily mean cure. For example, about 74 percent of liver cancer sites that had complete responses to first line chemotherapy showed evidence of recurrence within one year. In general, the absolute complete responses are about 4 percent.

There are several emerging areas in targeted oncology that may lead to significant changes in the landscape. One area is counting circulating tumor cells in colon cancer. The number of circulating tumor cells appears to be a stronger predictor of progression free and overall survival than age, performance status, or number of previous treatment regimens.

Another area of significant work is cancer stem cells. These are the cells that generally will not be eliminated by chemotherapy and subsequently these cells will give rise to other cells and tumor regrowth. The new cancer growth will no longer respond to treatments. Measurement of stem cell markers is being used to predict cancer recurrence. Presence of cancer stem cells may lead to longer duration of chemotherapy or use of suppressive agents like tamoxifen is used in breast cancer.

Another area of much research is modifying the immune system. Immunotherapeutic agents such as vaccines or immuno-stimulants are going to emerge as the next phase of revolution in oncology treatments.

Conclusion

Numerous targeted therapy agents are currently available and many more are in various stages of development. Many of these agents will be coming to market in the next few years. The paradigm of cancer treatment is clearly changing from a palliative to a curative, at least in some cancers, approach. If care is palliative, the emphasis on therapy is maintaining quality of life. The introduction of oral targeted therapies, rather than injectable agents, is very important in improving patient’s quality of life. Oncology is also changing from empiric therapy to predictive therapy. Predicting the patients most at risk of recurrence or most likely to respond to a particular agent is going to become the norm. JMCM

Edward H. Lin, MD is an associate member of the Fred Hutchinson Cancer Research Center, a part of the Seattle Cancer Care Alliance. Dr. Lin also is an associate professor in the oncology division at the University of Washington.

References