Elmer Wachtel (American, 1864-1929). *Capistrano Mission.* Oil on canvas, 15" x 25.50". Courtesy of the Fleischer Museum, Scottsdale, Arizona.

What New Drugs, Biologics, and Treatment Approaches Show Promise in Breast Cancer?

The multiplicity of new interventions for breast cancer will challenge our capability to clinically evaluate them.

DR HORTOBAGYI

A number of new agents are being developed concurrently, including cytotoxins, hormonal agents, and biologic approaches (Table). There are a number of new anthracyclines, particularly liposomal anthracyclines. There are ongoing clinical trials with liposomal daunorubicin and liposomal doxorubicin. At M.D. Anderson, we developed liposomal anamycin, which is a new anthracycline that is not a p-glycoprotein substrate; in the laboratory, it is effective in doxorubicin-resistant tumors. It is unclear whether liposomal daunorubicin or liposomal doxorubicin is more effective than doxorubicin. However, the pharmacokinetics and toxicity profiles of the agents certainly differ. Thus, these liposomal agents might create some opportunities for different combinations and scheduling.

A number of antifolates are undergoing clinical trials, although I think that only edatrexate will survive for breast cancer. Other antifolates are currently undergoing investigation for *Pneumocystis carinii* infections and other indications.

The anthrapyrazoles, of which losoxantrone is the best known, continue to be investigated in clinical trials. This agent demonstrates response rates ranging from 50% to 60%, which are similar to and possibly exceed those of the standard anthracyclines. An ongoing clinical trial is comparing losoxantrone/ cyclophosphamide with doxorubicin/cyclophosphamide. Other anthrapyrazoles, including teloxantrone, piroxantrone, and CI-958, are also being studied in clinical trials. These other agents demonstrate no obvious advantage compared to losoxantrone in preclinical studies.

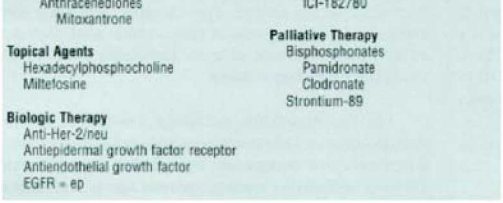
A large number of thymidylate synthase inhibitors are in clinical development. Raltitrexed and capecita-bine are completing phase II clinical trials and nearing initiation of phase III trials. Uracil/tegafur, S1, and a variety of others coming primarily from Japan are also under evaluation.

A number of agents inhibit the degradation of fluoropyrimidines. For example, Glaxo Wellcome has a compound (776C85) that has just entered phase II trials. There are new vinca alkaloids of which vinorelbine is the latest to be approved by the US Food and Drug Administration. However, there are at least two other new vinca alkaloids beginning phase I trials, primarily in Europe.

I am aware of one new taxane in clinical trials now and probably several that are approaching phase I trials. We have a hexadecylphosphocholine, miltefosine, that has been approved and is commercially available in Germany and other European countries. It is a moderately effective topical agent for local recurrences of breast and other tumors. Several camptothecin analogues appear to have some activity in breast cancer with reported response rates ranging from 15% to 25%. These include irinotecan (CPT-11), topotecan, and 9-aminocamptothecin (9-AC).

New Treatments for Breast Cancer

Spindle Poisons	**Vaccines**
Paclitaxel	
Docetaxel	**Angiogenesis Inhibitors**
Vinorelbine	$\alpha_v\beta_3$ integrin antagonists
	Matrix metalloproteinase inhibitors
Liposomal Delivery	Urokinase plasminogen activators
Doxorubicin	Platelet factor 4
Daunorubicin	Endostatin
Anamycin	Thrombospondin
	Vitaxin
Antifolates	Marimastat
Edatrexate	
Trimetrexate	**Antimetabolites**
Thymidylate synthase inhibitors	Gemcitabine
Raltitrexed	
Capecitabine	**Aromatase Inhibitors**
Uracil/tegafur	4-OHA
S1	Fadrozole
ZN93311	Vorozole
LY231514	Letrozole
	Anastrozole
Topoisomerase Inhibitors	
Topo I/Camptothecin analogues	**Other Hormonal Treatments**
Topotecan	GnRH agonists
Irinotecan (CPT-11)	Goserelin



At least two important monoclonal antibodies are directed at growth factors or growth factor receptors in clinical trials, including anti-HER-2/neu (4D5) and antiepidermal growth factor receptor (EGFR; C225). There are several other monoclonal antibodies against other components of epithelial cells that also are in clinical trials.

At least six different vaccines are being developed against breast cancer. A large number of agents have been developed to reverse MDR-mediated drug resistance, and a number of genetic modification approaches are in clinical trial. We have an anti-HER-2/neu transcription repression method that already has accrued five patients in a phase I clinical trial. We have a p53 transfer program using a retroviral method. We have also recently completed a phase I study transfecting the MDR-gene into hematopoietic stem cells to allow posttransplant cytotoxic therapy.[1]

Thus, there are many ongoing research trials and with the potential number of combinations and permutations, the possibilities are infinite.

DR SLEDGE

We have been very interested in another area, angiogenesis inhibitors. When I look in our chemotherapy tool box, it seems we are always waiting for that one chemotherapeutic agent to cure breast cancer. I believe we may wait a long time if we seek one particular drug to be the answer. I am impressed with the idea that we may be able to subvert the tumor's microenvironment rather than just simply kill the tumor. Fascinating data have come from Judah Folkman's group in recent years.[2,3] Basically, in the setting of micrometastatic disease, the tumor is already actively dividing but is held in check because it lacks an appropriate vasculature to allow growth. The tumor becomes capable of aggressive growth when it is able to induce real blood vessel growth into the tumor microenvironment. This angiogenic activity may occur at any point in the life of the tumor.

There are a number of approaches to subvert the tumor microenvironment and shut down the angiogenic process. These include drugs that will block the ligands for blood vessel-growth factor receptors, including $alpha_V beta_3$ integrin antagonists. Since $alpha_V beta_3$ integrin is essentially found only on proliferating vascular epithelial cells. In the laboratory, one can induce apoptosis in these cells using an antagonist to $alpha_V beta_3$ integrin. This drug will soon be entering clinical trials.

The matrix metalloproteinase inhibitors are important potential inhibitors of the angiogenesis process. The urokinase plasminogen activator family also is another target that may be useful in terms of the angiogenic process. Platelet factor 4 is another target that is being evaluated in the angiogenic process. Overall, there are eight or 10 different parts of the angiogenic process that represent potential therapeutic targets.

I believe that lack of knowledge on how to use these novel biologic approaches will be the primary investigational problem. We may have great difficulty testing these approaches in our current paradigm of testing drugs in metastatic disease. One cannot really expect that these drugs are going to affect a 2-kg tumor with a fully developed vasculature. However, one could easily rationalize evaluation of these agents in a micrometastatic disease setting, which might be similar to giving insulin to a diabetic. In other words, these agents may not cure the disease but potentially will allow the disease to be kept in check indefinitely. Thus, knowing how to test these agents will be a major challenge in the next few years.

Another important treatment approach comes from a different direction than new drugs. Specifically, I think learning how to select the drugs appropriate for each individual patient is an important area of research and has been a recurring theme in our discussions. An interesting example of this is the anti-HER-2/neu product. We have known for many years that HER-2/neu is a reasonable prognostic factor in breast cancer. In a micrometastatic disease setting, patients who are HER-2/neu-positive are more likely to relapse and die than those who are HER-2/neu-negative. As such, HER-2/neu has joined the exhaustive list of prognostic factors in breast cancer.

However, the interesting thing about HER-2/neu is that it may be a *predictive* as well as prognostic factor. It may define who responds to a particular therapy. In the metastatic hormonal therapy setting, for instance, a HER-2/neu-positive patient is highly unlikely to respond to hormonal therapy, regardless of hormone receptor status. In the adjuvant setting, in the spinoff trial from the CALGB trial that evaluated dose intensity, the only patients who benefited from high-dose doxorubicin-based chemotherapy were patients who were HER-2/neu-positive.[4]

Thus, in the future, we may be able to use an oncogene such as HER-2/neu or other factors to predict who will benefit from our standard regimens. Theoretically, this should allow our standard regimens to be used in patients most likely to benefit and allow us to avoid treating the patients who will experience only toxicity. In the future, we may be able to segment our breast cancer population into several different subgroups for whom particular therapies will be most effective. We have always done this with hormone receptors, but increasingly I think we are going to do this with these new predictive factors.

DR ROWINSKY

As far as the classic cytotoxic agents are concerned, the next very active agents that we are testing in San Antonio are the thymidylate synthase inhibitors. As Dr Hortobagyi mentioned, at least one or two of these agents, particularly raltitrexed, has demonstrated activity in breast cancer. Other thymidylate synthase inhibitors, including ZN93311 and LY231514, also are currently undergoing evaluation in breast cancer. These drugs are very different in structure and pharmacologic activity. I think we are going to see a number of trials that attempt to determine the roles of these agents in a number of other tumors.

We are close to evaluating clinically a number of agents directed against proliferative signaling. Two or three compounds will soon begin clinical trials. These compounds may prove very exciting and valuable. Another active agent of interest is gemcitabine. We are likely to see increasing evaluation of this drug both alone and in combination in a number of tumor types, including breast cancer. For example, we have just completed a phase I trial of gemcitabine plus paclitaxel in which we were able to administer both drugs using full single-agent doses.

phase I and II clinical trials. Long-term adjuvant studies with large patient numbers are required with long follow-up periods in order to truly understand the roles of these agents in cancer treatment.

References

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