



## Chemotherapy Principles for Breast, Prostate, Colon and Lung Cancer

By Michael Keppen, MD

### **Breast Cancer**

The complexities of cytotoxic chemotherapy and related systemic therapies for breast cancer can serve well as the paradigm for the treatment of all solid tumors. No type of cancer has been studied so extensively, has as many published clinical trials or has such well-developed multi-institutional clinical trial organizations. Breast cancer leads the way in the practical development of “personalized therapy,” based on genetic and biochemical markers obtained from each unique tumor specimen that lead to the choice of treatment that is the most active against that tumor.

Systemic therapy for breast cancer can be used as initial treatment (neoadjuvant), which is usually in larger tumors, often with palpable lymph node involvement, that would be difficult to resect with clear margins. More commonly systemic therapies are given after definitive surgical resection (adjuvant therapy) in an effort to eradicate micrometastatic disease and, hence, increase the cure rate of resected breast cancer. Systemic therapies are also employed in sequence for widespread metastatic disease found either at presentation or more commonly as relapsed disease.

The first trials of cytotoxic chemotherapy began to accrue patients in 1958, when Nissen-Meyer and colleagues in a randomized controlled study gave alkylating agents such as cyclophosphamide in a single dose in the immediate post-operative period, often in the surgical recovery room. The rationale was to eliminate “seeds” of microscopic disease that were disseminated during the operative manipulation. These studies showed a survival advantage for the treatment group for up to 20 years.

Modern multiagent clinical trials given over prolonged periods of time began in the late 1960s, with a hypothesis that breast cancer was often a systemic disease at diagnosis. The Early Breast Cancer Trialist’s Collaborative Group analyzes hundreds of these trials, with tens of thousands of participants, at five-year intervals. Analysis of these trials, including several published meta-analysis have led to several basic principles regarding chemotherapy:

1. Chemotherapy programs of six months or less are as effective as longer trials ranging from nine to 24 months;
2. Adjuvant chemotherapy verses no chemotherapy demonstrates absolute survival advantage with chemotherapy in all age groups under age 70, regardless of estrogen receptor status, menopausal status or stage of disease;

3. Earlier trials accrued too few women over age 70 to provide statistical power to analyze the survival effects of chemotherapy in this group;
4. Anthracycline-containing chemotherapy regimens have lower relapse rates than other chemotherapies when HER2neu status is not available for review; and
5. Taxane, when added to anthracycline-containing chemotherapies in node-positive patients, confer additional relapse-free survival advantage.

Aggressive, high-dose intensification was attempted for higher risk breast cancer patients during the 1990s and included studies using reinfusion of autologous bone marrow or peripheral stem cells. Presentation at the American Society of Clinical Oncology in 1999 of three pivotal randomized studies showed no survival advantage in any of the studies. The Duke University trial showed a trend for fewer relapses of breast cancer with high-dose therapy in women with 10 or more positive lymph nodes at initial diagnosis. Unfortunately, a 5 percent treatment-related mortality in the year following high-dose treatment negated any advantage towards survival. These studies have led to the abandonment of very-high-dose therapies as a method for improving survival.

Mathematical approaches to study design, led by Larry Norton, MD, at Memorial Sloan-Kettering Cancer Center, have resulted in clinical trials supporting a dose-dense approach to adjuvant therapy for breast cancer. The use of neutrophil colony stimulating agents such as filgrastim allows chemotherapy to be given in shorter intervals. When chemotherapy doses are divided by the units of time over which they are administered the dose intensity is similar to previous high dose regimens but without the severe morbidity. Further studies of this dose dense/dose intensity approach involve the weekly or even daily administration of chemotherapy (metronomic chemotherapy) in regimens that resemble some of the earliest successful adjuvant chemotherapy regimens of the 1970s, such as the Cooper regimen, with the daily administration of oral cyclophosphamide tablets.

Adjuvant chemotherapy programs of the future will rely less on "fine tuning" schedules or by adding newer conventional cytotoxic agents and more on the addition of targeted molecular agents, such as the monoclonal antibody trastuzumab (Herceptin), which binds and blocks the HER2Neu growth factor receptor on the cancer cell surface. After demonstrating remarkable activity in metastatic breast cancer in the traditional poor prognosis HER2Neu positive cancers, trastuzumab, added to taxane chemotherapy, has resulted in improved disease-free survival in the post-operative adjuvant setting as well. Transient cardiotoxicity has eliminated the use to trastuzimab concurrently with anthracycline chemotherapy but it appears the two drugs

can be given in sequence safely. The initial trial demonstrating advantage for trastuzumab arbitrarily picked one year of administration, which now remains the standard of care in the U.S.

Another agent targeting the HER2Neu complex is lapatinib, a small molecular inhibitor of the tyrosine kinase, which is part of the signal transduction pathway to the nucleus from the stimulated her2Neu receptor. The small molecular nature of this agent allows oral ministration rather than the cumbersome intravenous infusions of monoclonal antibodies. Small molecules also cross the blood brain barrier and may prevent brain metastases, an Achilles heel of large molecules such as trastuzumab-based adjuvant programs. A major clinical trial addressing trastuzumab and chemotherapy, lapatinib and chemotherapy, or a combination of chemotherapy, trastuzumab and lapatinib will help answer these important questions.

The treatment of metastatic disease in breast cancer as well as other solid tumors serves as the proving ground for new drugs and concepts in cancer therapy. As new agents demonstrate better response rates or survival advantages, they can be moved to adjuvant clinical trials in which their impact on cure rates can be measured. Major classes of drugs such as the anthracyclines, taxanes and HER2Neu inhibitors all entered the standard adjuvant programs in this manner. The monoclonal antibody against circulating vascular endothelial growth factor (VEGF) bevacizumab (Avastin) has demonstrated improved activity in metastatic breast cancer when added to the taxane paclitaxel in a single randomized study comparing the regimen to single agent paclitaxel alone. While this activity from a new agent in metastatic disease suggests the addition to adjuvant chemotherapy treatment of breast cancer, similar activity of bevacizumab in metastatic colon cancer did not improve survival in an adjuvant colon cancer trial. The activity of VEGF and angiogenesis may not be as important in small micrometastases, so the addition of anti-VEGF agents to future adjuvant programs will require rigorous clinical trials.

One of the most controversial questions in breast cancer chemotherapy is the role of the anthracyclines such as doxorubicin (Adriamycin) in the adjuvant setting. Meta-analysis of studies prior to anti-HER2Neu therapies confirmed the advantage of anthracycline-containing regimens, such as Fluorouracil, Adriamycin and Cyclophosphamide (FAC), Adraimycin and Cyclophosphamide (AC), and Fluorouracil, Epirubicin and Cyclophosphamide (FEC) over non-anthracycline regimens. Cardiac toxicity, in the form of cardiomyopathy and reduced left ventricular ejection fraction, occurs in a relatively small number of patients in short term follow-up. SEER review of Medicare patients suggests a very high incidence of congestive heart failure in patients with a

history of anthracycline adjuvant chemotherapy for breast cancer. This previously unrecognized late cardiac toxicity has led some thought leaders in oncology to question the need for anthracyclines in the light of retrospective analysis of HER2Neu status in previous clinical trials of anthracycline versus no anthracycline chemotherapy. When HER2Neu patients are eliminated from the analysis there is no difference in relapse, suggesting that all the benefit of anthracyclines was in the HER2NEU population. Since anti HER2Neu therapies also benefit these patients, there may be no need for anthracyclines in the adjuvant setting. One trial performed by the largest private oncology group in the United States, U.S. Oncology, compared a non-anthracycline chemotherapy docetaxel (Taxotere) and cyclophosphamide (or TC) versus the American standard doxorubicin (Adriamycin) and cyclophosphamide or AC in patients with non-HER2Neu breast cancer in an adjuvant setting. Early follow-up suggest lower relapse in the TC arm, lending further support to the notion of eliminating anthracyclines in adjuvant therapy of breast cancer.

A long-standing difficult decision for breast cancer patients and their oncologists is whether to use chemotherapy at all in relatively favorable risk; estrogen receptor positive, node negative patients. The use of adjuvant anti-estrogen therapies in these Stage 1(T1N0M0) and Stage 2A(T2N0M0) patients reduce the risk of relapse to such low levels that for most patients the additional benefit in overall survival with the addition of chemotherapy may only be 2 to 4 percent. Analysis of the RNA expression pattern on paraffin preserved breast cancer has been correlated with previous National Surgical Adjuvant Breast Project (NSABP) clinical trials comparing Cyclophosphamide, Methotrexate and Fluorouracil (CMF) chemotherapy plus tamoxifen with tamoxifen alone. A gene profile score on 16 relevant genes with an additional five control genes yields a score that distinguishes three groups: a low score correlates with good prognosis with antiestrogen therapy alone and virtually no additional benefit from chemotherapy, thus allowing patients to avoid the toxicities and expense of cytotoxic chemotherapy. Another group is characterized by a high score, which identifies a poor prognosis group which clearly benefits from chemotherapy based on the data set of NSABP patients. An intermediate group is still unclear as to the benefit of chemotherapy and is the subject of an ongoing randomized prospective trial (TailorRX) that aims to better answer this question. The RNA expression test called OncotypeDX is FDA-approved and is being widely used in clinical practice as part of the trend of “personalized” medicine in oncology.

As new targeted molecular therapies are developed in breast cancer, such as poly (adenosine-disphosphate-ribose) polymerase (parp) inhibitors, the future treatment may no longer be termed “chemotherapy” in the conventionally

held sense of crude cytotoxic drugs, but instead will be best characterized as systemic targeted molecular therapies based on DNA arrays, RNA expression and other biochemical markers of each individual cancer. Strong support of clinical trial participation by breast cancer patients will be needed to bring this future to all patients.

### **Prostate Cancer**

Prostate cancer, like breast cancer, is sex hormone-influenced and shares many clinical characteristics, such as the propensity for bony metastasis. Unlike breast cancer, prostate cancer was largely ignored from clinical trials for over two decades, in part due to a clinical trial system dependent on bi-dimensional measurable disease for treatment assessment. Prostate cancer with a propensity for bone metastases was excluded from many trials. Dependence on anti-androgen therapy provided only temporary relief until androgen resistance developed.

A clinical trial designed to measure quality of life and survival advantage, the preferred parameters of the FDA and NCI, as well as the recognition of PSA as an excellent surrogate for disease response, has allowed clinical trial development that recognizes the activity and benefits of treatment for prostate cancer.

Two agents are FDA-approved for use in prostate cancer. Mitoxantrone, an anthracycline that also has activity in breast cancer in conjunction with low-dose prednisone, has been shown to reduce bone pain and increase the quality of life in metastatic prostate cancer compared to a control arm of best supportive care. No survival advantage was seen in this trial, though survival was nor a primary endpoint.

Docataxel (Taxotere) has the highest single-agent activity in prostate cancer. A clinical trial of docataxel versus a control arm of mitoxantrone provided evidence of superiority in docetaxel in response rate and more importantly in survival, the first chemotherapy agent to do so in androgen-resistant prostate cancer. Docataxel will be the backbone of future clinical trials adding targeted molecular agents, such as the recently completed randomized trial adding anti-angiogenesis antibody bevacizumab versus placebo to docataxel. The potent parenteral bisphosphonate zoledronic acid (Zometa) is an additional component of care for the common problem of bone metastases. Cultural barriers regarding any treatment continue to slow the development of systemic treatment for androgen-resistant prostate cancer. The possibility of benefit from adjuvant chemotherapy after curative intent resection will need to be determined in future clinical trials.

### **Colon Cancer**

Chemotherapy for colon cancer developed more slowly than breast cancer, due to the delay in finding a chemotherapy agent with any clinically important activity. Not until

studies showed the agent folinic acid helped 5-fluorouracil (5-FU) bind more tightly to thymidylate synthetase was an active chemotherapy with meaningful clinical activity in metastatic colon cancer. The 5-FU/folinic acid combination was the first adjuvant, post-operative therapy to show benefit in node-positive (Stage 3) colon cancer. Studies were underpowered to determine benefit in Stage 2 patients until a large meta-analysis published in 2004 suggested a 2 percent improvement in DFS.

Chemotherapy for metastatic disease in the 5-FU-alone era resulted in median survival of about eight months in the U.S. The addition of a topoisomerase inhibitor-class drug, irinotecan, demonstrated a small improvement in survival. The rapid succession of new drugs in colon cancer from 2001 to 2004 included oxaliplatin, a drug with unique cold-induced neuropathy, bevacizumab, an antiangiogenesis drug targeting VEGF (vascular endothelial growth factor) and cetuximab, an antibody blocking the epithelial growth factor receptor (EGFR). Various combinations of these new agents has resulted in up to 10 percent complete response in metastatic disease, median survival of nearly 36 months (compared with eight months in 1990) and five-year survival rate in metastatic disease of about 30 percent. Patients with completely resected solitary lung or liver metastases, followed by further adjuvant chemotherapy and biologic agents, can achieve up to 40 percent five-year survival rates as determined by large single-institutional trials.

Future directions in clinical trials will explore the optimal sequencing and combinations of the seven current FDA-approved drugs for colon cancer: 5-FU; capecitabine, an oral 5-FU prodrug, irinotecan; oxaliplatin; and the two monoclonal antibodies to EGFR cetuximab a mouse human chimera AB and panitumumab, a fully humanized monoclonal AB. Prolonged survival is tightly linked to patients receiving all three chemotherapy classes as well as a biologic agent. Of-note attempts at combining monoclonal agents together, i.e., bevacizumab and an EGFR inhibitor, have resulted in inferior survivals suggesting an unfavorable response.

Personalized therapy in colon cancer includes the determination of any mutations in codon 12 or 13 in the *kras* gene present in colon cancer. Virtually all responses to the EGFR antibodies occur in unmutated "wild type" *kras*, thus sparing patients with mutated *kras* an expensive and potentially toxic therapy with little chance of benefit. Other personalized options include the determination of mutations in the dihydropyrimidine dehydrogenase activity, the enzyme responsible for clearing active metabolites of 5-FU. Heterozygotic mutations result in severe gastrointestinal mucosal injury and homozygotic mutations can lead to lethal complications.

The chemotherapy agent irinotecan, a topoisomerase

inhibitor, is metabolized by a member of the UDP glucosyltransferase superfamily, *AUGTIAI\*28* which can be mutated to a form associated with slow metabolism and increased gastrointestinal and hematologic toxicities in 9 percent of the North American population. Major dose reductions are needed in homozygote mutations, these patients may be identified by mild elevations in indirect bilirubin, Gilbert's syndrome, which is also associated with this mutation.

The same biotechnology company, which designed the OncotypeDX genomic assay in breast cancer, has developed an 18-gene analysis of Stage 2 colon cancer, which currently identifies a group at twice the risk for relapse after surgery. Future trials may identify favorable-risk Stage 2 patients who can forego chemotherapy since the absolute benefit may be very small with chemotherapy.

### Lung Cancer

Chemotherapy of lung cancer is a challenge, since this cancer is highly lethal and is the number one cancer killer in the U.S. Small cell lung cancer is potentially cured in a small subset of patients with disease limited to the central thorax that can be treated simultaneously with chest radiation. Little has changed in the last 20 years with cisplatin and etoposide as the preferred chemotherapy. Curative advances have largely been due to the better integration of radiation early in the chemotherapy treatment, as well as the widespread use of prophylactic brain radiation to prevent relapse in the brain due to its pharmacologic sanctuary status provided by the blood brain barrier to non-lipophilic drugs. Patients with widespread, extensive stage, small cell lung cancer are offered short-term survival advantage by chemotherapy but little progress has been made since the 1980s, and virtually all of extensive stage patients will die of their disease in two to three years.

Chemotherapy in non-small cell lung cancer usually based on platinum or taxane drug couplets, has been shown to improve quality of life compared to best supportive care. Survival advantage with the various chemotherapy combinations for non-small cell cancer are measured in weeks to a few months. The addition of the same biologic agents that have improved survival in metastatic colon cancer, have also benefited non-small cell lung cancer patients but with more modest benefits.

Personalized therapy in lung cancer involves histological, genomic and demographic information. Squamous histologies are associated with poor response rates to the multitargeted antifolate, pemetrexate. Squamous cancers, which are more often centrally located than adenocarcinomas, are associated with high risk for lethal pulmonary hemorrhage with use of anti-angiogenesis therapies and are thus contraindicated. Bronchoalveolar cancers are more likely to

respond to tyrosine kinase inhibitors of the EGFR pathway, erlotinib and gefitinib, as are non-smokers, women and patients of Asian descent. EGFR receptors on non-small cell lung cancer have identified a group which responds to cetuximab, the EGFR antibody but this drug is not yet FDA-approved for use in lung cancer.

Like colon cancer, the evolution of adjuvant chemotherapy after curative resection of non-small cell lung cancer was hindered by the lack of effective chemotherapy regimens. The platinum-based chemotherapies have now been shown to offer improvements in disease-free survival in patients with Stage 1B, 2 and 3A who have been completely resected. Absolute survival advantage is small, at 2 to 4 percent increase, with the greatest advantage for Stage 2 patients with peribronchial and perihilar involvement. The costs and morbidities of therapy, along with the still-disappointing cure rates, suggest that pharmacologic "cures" of tobacco smoking may have as much future promise as further incremental advances in the systemic treatment of this most lethal, yet preventable, cancer.

As cancer chemotherapy, biologic therapy and other targeted molecular therapies evolve, current state-of-the-art treatments for cancer can be reviewed at three Web sites:

- [www.cancer.gov](http://www.cancer.gov) is the National Cancer Institute (NCI)-sponsored site that provides information to both patient and professionals for all common cancers and provides links to the available NCI sponsored clinical trials;
- [www.nccn.org](http://www.nccn.org) is compendium of guidelines for most cancers as determined by panels of experts from the largest NCI-sponsored cancer center in the U.S. This has become the mostly widely recognized standard of care for cancer care in the U.S.; and
- [www.adjuvantonline.org](http://www.adjuvantonline.org) is an online tool to help patients and clinicians make decisions on adjuvant therapy using clinical, biologic, demographic and genomic data from individual patients and helps put complex statistical information in a easily understood graphic form.

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