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## Oncologists & Cardiologists Joining Together to Tackle Cardiotoxicity

BY DANIEL M. KELLER, PHD

Oncologists worry about chemotherapy-related heart failure, and cardiologists treat it. Efforts are now under way to bring the two camps together to better understand the mechanisms involved, monitor cardiac function in cancer patients, treat heart failure when it occurs, and develop prevention strategies.

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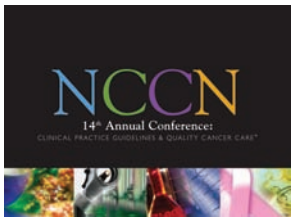

**Panel Struggles to Put a Value on Cancer Care** p. 20

PERIODICALS

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# NCCN Panel Struggles to Put a Value on Cancer Care

BY ED SUSMAN


HOLLYWOOD, FL—As the world economy struggles to rebound, the concept of placing a value on medical outcomes has risen to the top of agendas in public and private quarters. Trying to get a grip on value in providing oncologic outcomes, though, proved elusive for a panel here of physicians, doctors, insurers, pharmacology marketers, and others during the National Comprehensive Cancer Network's Conference on Clinical Practice Guidelines and Quality Cancer Care.

"We are living in turbulent times economically, and the notion of value has taken on special meaning," said the moderator, Clifford Goodman, PhD, Senior Vice President of the Lewin Group, a health care policy consulting firm based

in Falls Church, VA. "Increasingly, the economic component is entering value in health care—or some might say—encroaching upon it."

For Lee N. Newcomer, MD, MHA, Senior Vice President of Oncology Services at UnitedHealth Group and Chairman of the Board of Park Nicollet Health Services in Minneapolis, value in cancer care involves outcomes: "Are we making some kind of improvement in survival?"

He said he was not confident that doctors can define value. "If I were to go to an oncology group and say I would like to know your survival for any given disease and your average cost for getting there, I don't think there is anyone in the United States who could tell me," Dr. Newcomer said. "We have tried to measure their performance and we find it very difficult to come up with an average cost."

> "We are living in turbulent times economically, and the notion of value has taken on special meaning, causing a focus on costs associated with treatment that has never been there before."

He suggested that the economic downturn will drive consumers to be willing to give up some choice in order to ensure the certainty of some medical coverage.

### 'Relatively New Phenomenon'

"The question about value in oncology care is a relatively new phenomenon—just in the last four to five years," noted Joseph S. Bailes, MD, Chair of the American Society of Clinical Oncology Foundation. "There certainly has been no explicit recognition of costs. I think there is a lot of opposition to putting costs in the equation. We are a long way away from that.

"The current economic conditions, however, are causing a focus on costs associated with treatment that has never been there before."

### 'Can't Define'

Stephen B. Edge, MD, Chair of Breast Surgery at Roswell Park Cancer institute and Professor of Surgery at the State University of New York at Buffalo, said, "The medical community can produce information on who was treated for cancer and what their care was and outcomes were, but we can't define value."

"Cost outcomes are objective," observed A. Mark Fendrick, MD, Professor of Internal Medicine at the University of Michigan. "We can all measure them. Value is subjective and that's where the rubber meets the road."

Dr. Fendrick, Editor of the *American Journal of Managed Care*, said, "Individuals at this table haven't been asked about value until very recently. If you want it, you have to ask for it. Most of us wouldn't buy our laptop computers, our cars, and even our neckties if we didn't have information on cost and quality."

He said that patients are being affected by the economy by cutting back on prescription filling and doctor visits. "People are not doing the right things and are not doing the wrong things equally because the system does not incentivize them to do the right thing. Senator Ted Kennedy stated in 1974 that we would not have a health care crisis if we paid only for things that produce health. I think the idea is that if we get the information to find those interventions that produce health, we will get us all on a better track."

Part of the problem in getting on the right track is trying to get a handle on costs—and costs are driven by new technologies and end-of-life treatments. Lynn Zonakis, Managing Director of Health Strategy and Resources for Delta Air Lines, is responsible for the health care of 200,000 individuals under the Delta-Northwest wings.

"It is really the size of a small health plan," she said. "Of the 82,000 active plan participants under Delta's care, 449 people are driving 77% of the costs. What that tells you is that people like me are very focused on the care of the sickest and how we are going to manage that when we only have so many dollars. Cancer is driving

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# GI Cancers Symposium: Research Highlights

## Advanced Gastric Cancer, Esophageal Adenocarcinoma, Pancreatic Cancer Biomarkers, Reducing Pamitumumab-Related Rash

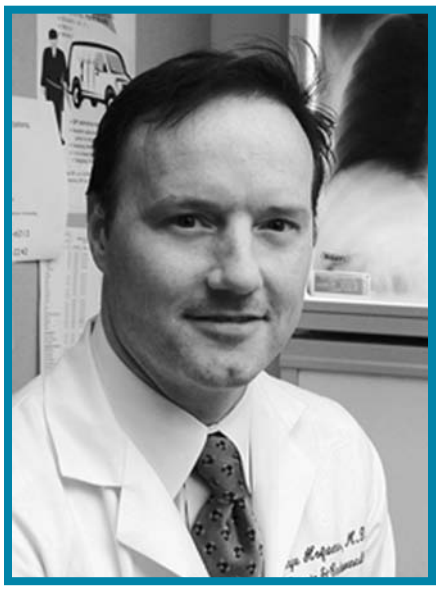
BY RABIYA S. TUMA, PHD

SAN FRANCISCO—Two randomized trials testing drug combinations with the oral fluoropyrimidine S-1 failed to improve overall survival in patients with advanced gastric cancer, according to data presented here at the Gastrointestinal Cancers Symposium. An uncontrolled Phase II trial testing a modified docetaxel, cisplatin, fluorouracil (5-FU) and bevacizumab regimen showed promising results.

The meeting is cosponsored by the American Gastroenterological Association Institute, the American Society of Clinical Oncology, the American Society for Radiation Oncology, and the Society of Surgical Oncology.

In the FLAGS study, Jaffer A. Ajani, MD, Professor of GI Medical Oncology at the University of Texas M. D. Anderson Cancer Center, and colleagues randomly assigned 1,053 patients to treatment with either 100 mg/m$^2$ of cisplatin on Day 1 plus 1,000 mg/m$^2$ of 5-FU continuous infusion on Days 1-5 every four weeks or 75 mg/m$^2$ of cisplatin plus 25 mg/m$^2$ S-1 twice daily on Days 1-21 every four weeks.

Although the S-1 regimen was associated with significantly less toxicity than the 5-FU arm, there was no increase in median overall progression-free survival (4.8 vs 5.5 months in the S-1 and 5-FU arms, respectively) or in overall survival (8.6 vs 7.9 months).



WAYNE HOFSTETTER, MD: "We are still advocating multimodality therapy for patients with esophageal adenocarcinoma, but in situations where patients have had definitive chemoradiation—for whatever reason—and they do have recurrent locoregional disease, they should be offered salvage esophagectomy."

Although the outcomes appear similar, Robert J. Mayer, MD, Director of the Center for Gastrointestinal Oncology at Dana-Farber Cancer Institute and Professor of Medicine at Harvard Medical School, who discussed this group of abstracts, noted that the study was not powered for equivalence or non-inferiority and thus all that one could conclude was that the S-1 regimen was not superior.

When asked during the question-and-answer period why the researchers did not use a non-inferiority design, Dr. Ajani said they had asked the Food and Drug Administration to approve a non-inferiority trial design, but the agency had declined. The questioner followed up asking, "So it was a political decision and not a scientific one?" Dr. Ajani replied succinctly: "No comment."

A more serious problem with the trial design in Dr. Mayer's view, however, is the difference in cisplatin doses between the two arms. "It should have been superior. S-1 has two additional mechanisms of action. But if you don't have an equitoxic program, it raises an enormous question," Dr. Mayer told *OT*.

"The fact that there was 25% less cisplatin may have been all the difference. I don't know that that study is really negative,

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at least a quarter of that cost."

Dr. Edge noted that all of the NCCN guidelines struggle with the question of end-of-life treatment: "I am not sure that we can answer this question any better than anyone else in this room regarding the cost of end-of-life care."

"It may be up to organizations such as the NCCN to write end-of-life care guidelines rather than allow a government agency to do it."

### 'Value-Based Insurance Design'

Dr. Goodman said that he thought that the need to find answers to value is going to get more intense as third party payers start investigating the concept of value-based insurance design.

If such a system were in place at UnitedHealth Group, Dr. Newcomer said he could see it being applied in various ways. He used treatment for breast cancer with trastuzumab as an example: "Trastuzumab is a wonderful drug that reduces relapse rates by 50%," Dr. Newcomer said. "There should be zero co-payment in using trastuzumab in the adjuvant setting. When you are in the metastatic setting, trastuzumab is far less effective in terms of prolonging outcomes. So, because its outcome is not so good, let's raise the co-payment there. And maybe a few women decide not to use it even though it is an effective drug that will give them some benefit."

Dr. Fendrick said he could envision a value-based insurance design working something like this: "Fifty-year-olds should get a colonoscopy for free, but if you are a 29-year-old with no family history of colon cancer, you should pay 100% of that cost for a colonoscopy because there is no benefit and you should be fined $500 for taking your mother's spot."

He said that one of the problems in seeking value in oncology has been that at present "we are talking about other people's money. I think that if the doctor and the patients were spending their own money, none of this would be of public concern. People want to have their money collectively spent more wisely.

"We need more critical information, without question."

### 'Usefulness Increases Over Time Where Price Doesn't Change'

Scott Gottleib, MD, an attending physician at Stamford (CT) Hospital and a resident fellow at the American Enterprise Institution, said, "When it comes to price, I don't have a solution on health pricing, but I do have an observation: In my view the health market is the only place where you have a product whose usefulness increases over time where the price doesn't change.

"The problem is that you want to start at a fixed price that is the highest you can get in the market," he continued. "You are forced to test these products in third-line and fourth-line settings in order to get them on the market, and you can't change the price once they are on the market even if you have demonstrated a lot of incremental value."

"What might be better is that if Genentech was paid on the basis of outcome, on a course of treatment. The pricing system creates perverse incentives. The incentives are not there to reduce the volume of drug used. I think there is an opportunity for private players to try to enter into value-based reimbursement schemes with some of the bigger drug companies.

"I don't think the government can take the lead in that. It is not creative enough, frankly," Dr. Gottleib said, adding that in the current economic climate the chance of greater government control in medical expenditure is higher than ever.

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as much as if you could go back and do it again, you might design it differently."

Meanwhile in a randomized Phase II trial comparing S-1 plus irinotecan versus S-1 plus paclitaxel, researchers from the Osaka GI Cancer Chemotherapy Study Group in Japan found that neither regimen increased the overall response rate to 50% in patients with advanced gastric cancer, which was the primary endpoint of the trial.

By RECIST criteria the response rate in 51 patients treated with irinotecan and S-1 was 33% compared with 31% in the 51 patients treated with paclitaxel and S-1. Patients treated with the paclitaxel combination had somewhat fewer adverse events, with hematologic adverse events more common in the irinotecan arm.

The median progression-free survival was 5.2 months and the median overall survival was 13.2 months for all patients combined.

Comparing these data with previous trials, the study authors suggested that the regimens have the potential to become the new standard of care in first-line therapy. However, during his discussion of the data, Dr. Mayer noted that the overall survival data were similar to overall survival reported previously with cisplatin combinations and thus he did not concur with their conclusion.

### Metastatic Gastroesophageal Adenocarcinoma

In a third abstract presentation, Manish A. Shah, MD, of the Gastrointestinal Oncology Service at Memorial Sloan-Kettering Cancer Center, and colleagues reported results from a Phase II single-arm study testing a modified docetaxel, cisplatin, 5-FU (mTCF) and bevacizumab regimen in patients with metastatic gastroesophageal adenocarcinoma.

A previous Phase III trial showed that TCF led to better response and survival rates compared with cisplatin and 5-FU alone, but that the three-drug combination led to an unacceptably high rate of Grade 3/4 neutropenia. Therefore, Dr. Shah and colleagues used a FOLFOX-like approach to reduce toxicity.

The 44 patients in the trial received 10 mg/kg of bevacizumab, 40 mg/m$^2$ of docetaxel, 400 mg/m$^2$ of 5-FU, 400 mg/m$^2$ of leucovorin on Day 1, 1000 mg/m$^2$ of 5-FU over 48 hours starting on Day 1, and 40 mg/m$^2$ of cisplatin on Day 3.

EDITH P. MITCHELL, MD: "We found that if we initiated this therapeutic regimen before starting panitumumab, we could decrease the more serious toxicities. All of our patients now receive preemptive skin treatment prior to starting panitumumab."

The six-month progression-free survival rate was 79%, which exceeded the primary aim of the study of a 63% six-month progression-free survival rate. Additionally 67% of the patients had a partial response by RECIST criteria, the median progression-free survival was 12 months, and median overall survival was 16.2 months.

The modified regimen was better tolerated than the parent regimen, with 51% of patients developing Grade 3/4 neutropenia and two patients (4%) developing febrile neutropenia.

"This is in stark contrast to the parent TCF in which the rate of febrile neutropenia was almost 30%," Dr. Shah said. The modified regimen was also associated with less gastrointestinal toxicity. However, the addition of bevacizumab may have introduced some new toxicities, with one patient having gastric perforation and 31% of patients developing venous thrombosis.

Dr. Shah concluded that the regimen was significantly better tolerated than the parent regimen and that "modified TCF plus bevacizumab demonstrates very encouraging survival."

Looking at the data from all three abstracts, Dr. Mayer concluded that although multiple treatment options are available for the treatment of patients with advanced gastric cancer, none of the regimens has shown itself to be clearly superior to the others.

### Salvage Esophagectomy Possible

Also presented in the same session were data indicating that salvage resection is relatively effective and safe for patients with esophageal adenocarcinoma who have locoregional disease after definitive chemoradiation. Although some surgeons hesitate to perform salvage resections in patients who have undergone definitive chemoradiation, the retrospective review of patients resected at M. D. Anderson found that patients who underwent salvage resection had outcomes similar to those who underwent planned surgery.

With a median follow-up of 24 months, the estimated five-year overall survival for the 45 patients who underwent salvage resection was 46% compared with 42% for the 300 patients who underwent planned esophagectomy.

The overall rate of postoperative complications was higher in the patients who underwent planned resection compared with those who underwent salvage resection (55% vs 40%), but serious complications appeared to be more common in the salvage resection group based on a higher rate of re-admittance to the intensive care unit (7% in planned vs 18% in the salvage group) and the salvage-resection patients had a higher 30-day mortality than those in the planned surgery group (6.7% vs 2.7%).

"We are still advocating multimodality therapy for patients with esophageal adenocarcinoma," said the lead investigator, Wayne Hofstetter, MD, Director of the Esophageal Program at M. D. Anderson.

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Someone asked in the question-and-answer period why the researchers did not use a non-inferiority design, and the reply was that they had asked the FDA to approve a non-inferiority trial design, but the agency had declined. The questioner followed up asking, "So it was a political decision and not a scientific one?" The reply came back: "No comment."

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The concept of paying on the basis of outcome is something his pharmaceutical company can live with, said Robert Mass, MD, Head of Medical Affairs for BioOncology at Genentech, which markets trastuzumab.

"I don't think this discussion about value makes me nervous," Dr. Mass said. "I think we can work with a system in which drugs are reimbursed at various prices depending upon their use.

"What real value is, is making progress in improving peoples lives. Those discussions over cost are best left at the bedside between the doctor and the patient. Our job is to provide the data so that we can give doctors and patients information they need to make those decisions. We provide clinical trials that demonstrate the effectiveness and then we set a price in the market place for our products that is based on the value.

"All we need is a system that is clear to everyone, and we can operate within that system. We set the price for bevacizumab based on its use in colon cancer. We do recognize that the drug has different effects in other cancers.

"We would like to see more consistent approaches for this more novel pricing for value-based insurance. It is easier to estimate value with a screening procedure. I think we struggle with what a patient gets in value in a metastatic environment. That is the value of a quality-adjusted life-year. We can measure quantity of time pretty easily but we can't necessarily measure the quality of that time very well."

Dr. Gottlieb said that he doesn't think it will get to a point in the US of putting a value on a life-year. "There is no will in Congress for that.

"If we do ever come up with a construct, I think it will just be used to extract price concessions on both the products and frankly, physicians' services. The people who are making decisions in Washington really don't have a systematic approach to it, and there is not a lot of quality clinical judgment going into what's going on," he said.

"It may be up to organizations such as the NCCN to write end-of-life care guidelines rather than allow a government agency to do it."