

# Chemo's Toxicity Averted With Cardiac Drugs

BY BRUCE JANCIN  
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SNOWMASS, COLO. — Administering an ACE inhibitor or carvedilol in cancer patients prior to high-dose chemotherapy is an excellent strategy for preventing chemotherapy-induced cardiomyopathy.

Chemotherapy-induced cardiomyopathy (CIC) is a far more common problem than most nononcologists appreciate, occurring in at least a quarter of patients on some widely prescribed regimens. Affected patients are not only exposed to the morbidity and mortality of heart failure, but their cancer therapy often has to be curtailed because of their cardiac impairment.

So rather than waiting for CIC to occur and then scrambling treat

it, why not prevent it?, asked Dr. John S. Schroeder, professor of medicine at Stanford (Calif.) University, asked at a conference sponsored by the Society for Cardiovascular Angiography and Interventions.

He cited two randomized trials that have paved the way. In one, Dr. Nihat Kalay and colleagues at Erciyes University, Kayseri, Turkey, randomized 50 cancer patients slated to start notoriously cardiotoxic anthracycline chemotherapy to carvedilol (Coreg) at 12.5 mg once daily or placebo. At 6 months' follow-up, the mean left ventricular ejection fraction (EF) in the carvedilol group was essentially unchanged from the 70% baseline figure, while in the control group it fell from 69% to 52%.

One patient in the carvedilol arm and five on placebo had an EF below 50% at 6 months. There was one death in the carvedilol arm and four among controls (J. Am. Coll. Cardiol. 2006;48:2258-62).

Oxidative stress and mitochondrial dysfunction are believed to figure prominently in the pathophysiology of anthracycline-induced cardiomyopathy. The Turkish cardiologists pointed to carvedilol's antioxidant effects—considered the most potent of any  $\beta$ -blocker—as the most likely mechanism for the drug's ability to prevent cardiotoxicity. They selected a relatively low dosage because patients had normal baseline ventricular function and carvedilol's antioxidant properties are manifest even at lower doses.

Dr. Schroeder agreed that carvedilol's strong antioxidant effects make it the  $\beta$ -blocker of choice for prevention of CIC. He added, however, that the prolonged-release formulation probably makes more sense.

The other key clinical trial in the prevention of chemotherapy-induced cardiomyopathy was conducted by Dr.

Daniela Cardinale and colleagues at the European Institute of Oncology in Milan.

Among 473 cancer patients with a normal baseline EF undergoing high-dose chemotherapy, they identified 24% as being at particularly high risk for CIC on the basis of a troponin I level greater than 0.07 ng/mL obtained within several days after completing any chemo cycle. The investigators randomized these 114 patients to 1 year of enalapril or to no enalapril beginning 1 month after the end of the final cycle of chemo. The ACE inhibitor was slowly titrated to 20 mg once daily.

**Carvedilol's strong antioxidant effects make it the  $\beta$ -blocker of choice for prevention of CIC.**

DR. SCHROEDER



The primary end point—a greater than absolute 10% drop in EF to a value below 50% at 1 year as assessed by blinded echocardiographers—occurred in 43% of controls and 0% of the ACE inhibitor recipients. In the control group there were 30 cases of the secondary combined end point of cardiac death, acute pulmonary edema, overt heart failure, or life-threatening arrhythmia, compared to just one in the enalapril group (Circulation 2006; 114:2474-81).

The Italians surmised that the observed benefits involved a class effect and any ACE inhibitor would probably be effective. Dr. Schroeder agreed, adding that there are few data regarding the use of angiotensin II receptor blockers for this purpose.

In an earlier study Dr. Cardinale and colleagues showed that an increased troponin I level shortly after a cycle of high-dose chemotherapy was a strong predictor of cardiotoxicity, while patients with a normal troponin I didn't develop ventricular dysfunction. The highest risk was seen in patients whose troponin I was elevated early and again 1 month later (Circulation 2004;109:2749-54).

Thus, serial troponin I monitoring allows for a selective approach to the use of drugs aimed at preventing cardiotoxicity.

But Dr. Schroeder indicated he did not like the idea of waiting to treat until the troponin elevation indicated the disease process was underway. His preference is to prevent the troponin rise by starting prophylaxis before chemotherapy.

It's worthwhile to get an EF measurement in the middle and at the end of each cycle of chemotherapy and hold the chemo should the EF fall by more than 10% from baseline, he advised at the meeting, also sponsored by the American College of Cardiology.

Dr. Schroeder is on the speakers bureau for several pharmaceutical companies, including GlaxoSmithKline, which markets carvedilol.

# Subclinical Hypothyroidism Linked to Heart Failure

BY JOHN R. BELL  
Associate Editor

NEW YORK — Subclinical hypothyroidism with a thyroid-stimulating hormone level of 10-20 mU/L was associated with an almost twofold risk of clinical heart failure in a study of more than 3,000 older adults.

The findings, presented by Dr. Douglas Bauer at the annual meeting of the American Thyroid Association, come from an analysis of participants in the prospective Cardiovascular Health Study, which includes persons from Medicare population-based listings at four university hospitals in the United States and is funded by the National Institutes of Health.

Dr. Bauer and his colleagues recruited 3,065 participants who were free of heart failure at baseline and not taking any medication known to affect thyroid function. Any participants who initiated T4 replacement during the study were removed from the analysis, and 21 were excluded because of insufficient serum for testing. Participants were followed for 12 years and were contacted every 6 months for assessment of outcomes, said Dr. Bauer of the University of California, San Francisco.

Of the 495 persons (16%) with hypothyroidism, 448 had a TSH level between 4.5 mU/L and 9.9 mU/L and 47 had a TSH level of 10-20 mU/L. Hyperthyroidism (TSH level below 0.45 mU/L and normal T4 value) was found in 44 persons. All hypothyroidism and hyperthyroidism in the study was subclinical.

Echocardiograms were obtained for all participants at baseline and at 5 years' follow-up and read by blinded clinicians (including cardiologists). Some participants experienced heart failure before the 5-year follow-up, and their clinical echocardiograms were also included.

At 12 years' follow-up, 660 persons (22%) had heart failure. In the 47 participants with a TSH level of 10-20 mU/L,

there were 45 heart failure events per 1,000 person-years, compared with 22 events per 1,000 person-years in euthyroid participants. Multivariate analysis showed an unadjusted hazard ratio of 2.03 for those with a TSH level of 10-20 mU/L, versus euthyroid participants—a significant difference. (Adjusted for confounding factors, the hazard ratio was 1.88.) No increase in heart failure risk was seen in the hypothyroid participants with TSH levels of 4.5-9.9 mU/L or in euthyroid persons, versus those with TSH levels below that range. There was no difference in the heart failure rate between men and women.

Moreover, at 12 years, impaired cardiac function was associated with TSH levels of 10-20 mU/L: The percentage of participants who had an abnormal left ventricular ejection fraction at time of incident heart failure was 80% in the high-TSH hypothyroid group, compared with 39% in the lower-TSH hypothyroid group, 44% in the euthyroid group, and 33% in the hyperthyroid group.

Dr. Bauer and colleagues concluded that "subclinical hypothyroidism is associated with a moderately increased risk of clinical events of congestive heart failure among older individuals with a TSH greater than 10 [mU/L]."

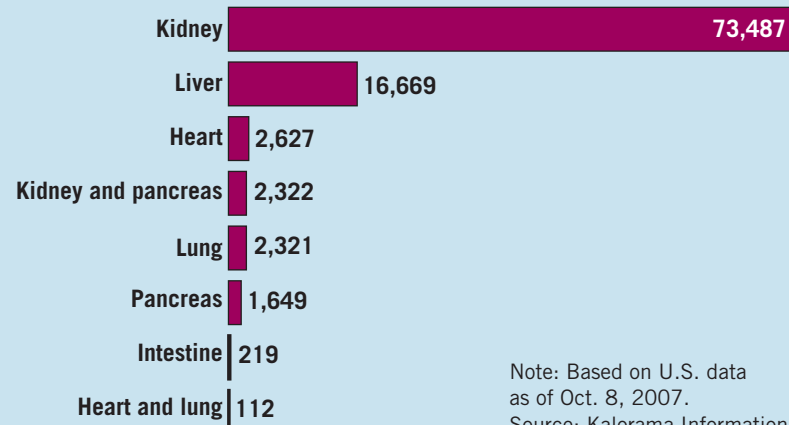
He acknowledged that the study was limited by a shorter follow-up period for the echocardiography data than for the heart failure data (5 years vs. 12 years), as well as missing follow-up echocardiograms for some participants.

Several studies have established an association between subclinical hypothyroid and hyperthyroid disease and cardiac dysfunction, Dr. Bauer said. But most studies have looked at subtle abnormalities in contractility, rather than at more clinically important measures, such as left ventricular ejection fraction. Also, most of those studies have been limited by small sample sizes and lack of randomization.

**Subclinical hypothyroidism is associated with a moderately increased risk of heart failure among older individuals with a TSH greater than 10 mU/L.**

## DATA WATCH

### Number of Candidates on Organ Transplant Waiting List



Note: Based on U.S. data as of Oct. 8, 2007.  
Source: Kalorama Information