CARDIOLOGY Rounds®

As presented in the rounds of the Division of Cardiology, St. Michael's Hospital, University of Toronto

Trastuzumab and Heart Failure

By WENDY TSANG, MD, and GORDON MOE, MD, FRCPC, FACC

Trastuzumab is a life-saving therapy in the treatment of breast cancer. However, its use is associated with the development of systolic dysfunction in 5% of patients and approximately 2% of these patients will develop symptomatic congestive heart failure. It is believed that a "2-hit" hypothesis is behind the mechanism causing cardiac dysfunction: activation of apoptotic pathways due to anthracycline or other cardiac stress, and loss of anti-apoptotic signaling due to trastuzumab use. Trastuzumab-related cardiac dysfunction is not dose-dependent and the majority of patients recover cardiac function with discontinuation of the drug and administration of standard cardiac therapy for heart failure. Trastuzumab can be safely reinitiated once cardiac function has recovered. This issue of *Cardiology Rounds* reviews the epidemiology, pathophysiology, and management of patients undergoing trastuzumab therapy. The utility of biochemical markers in predicting which patients develop trastuzumab-related cardiotoxicity and whether medications can be used to prevent its development will also be discussed.

Breast cancer is the most common female malignancy in the world, accounting for 22% of all new cancer diagnoses in women and >7.6 million cancer-related deaths worldwide.[1] In Canada, breast cancer is the most common cancer in women, with >22,000 new diagnoses every year.[2] Although it kills 5,300 Canadian women annually, due to advances in adjuvant therapy and greater participation in screening programs, breast cancer mortality is now declining. Since 1986, mortality has fallen 25%, from 32 to 24.1 per 100,000 in all age groups.[2] This means that an increasing number of women are alive with the diagnosis of breast cancer. It is estimated that 162,600 Canadian women who are alive today (or 1 in every 100 females) has had a diagnosis of breast cancer at some time during the last 15 years.[2]

One new agent that has been credited with increasing survival is trastuzumab or Herceptin® (Genentech). Trastuzumab is a humanized monoclonal antibody against the Her-2 oncogene. The HER2 protein is overexpressed in 20%-30% of breast cancers and is associated with a poorer prognosis.[3] In randomized clinical trials of metastatic breast cancer, the addition of trastuzumab to chemotherapy led to a significant improvement in response rates, increased time-to-treatment failure, and better overall survival (Table 1).[4,5] In the HER2-positive, early-stage, breast cancer trials involving over 13,000 women, the use of trastuzumab reduced the 3-year risk of recurrence by about 50%.[7-9] This is despite differences in patient populations, chemotherapy regimens, and sequence of treatments. These trials also revealed that mortality decreased by about one-third.[7-9] Trastuzumab is currently approved for use in the treatment of metastatic breast cancer and as adjuvant therapy in those with Her-2 positive cancers. Unfortunately, the use of trastuzumab has been associated with an increased incidence of congestive heart failure (CHF).[5,6]

Epidemiology

In the early studies in metastatic breast cancer, the overall incidence of heart failure due to trastuzumab was 22%, with 10% having New York Heart Association (NYHA) functional class III or IV symptoms.[5] The risk was higher in patients receiving anthracyclines

St. Michael's Hospital
30 Bond St.,
Suite 7049, Queen Wing
Toronto, Ont. M5B 1W8
Fax: (416) 864-5941

Table 1: Efficacy data from randomized trials with trastuzumab

Trial	N	Median overall survival (p-value)	Response rates (p-value)	Median time-to-treatment failure (p-value)
Slamon, 2001[5]	469	25.1 vs 20.3 months (0.0046)	50% vs 32% (<0.001)	7.4 vs. 4.6 months (<0.001)
Marty, 2005[4]	186	31.2 vs 22.7 months (0.0325)	61% vs 34% (0.0002)	9.8 vs. 5.3 months (0.0001)

concurrently with trastuzumab versus those taking trastuzumab alone, 27% versus 13%, respectively. Subsequent trials were designed to avoid concurrent anthracycline and trastuzumab use and their results suggest that the incidence of systolic dysfunction was approximately 5%, with 2% developing symptomatic congestive heart failure and 1% having NYHA functional class III or IV symptoms (Table 2).[4,7-10] Only one death was associated with the use of trastuzumab in these trials.[7] Risk factors for the development of cardiac dysfunction included previous or concomitant anthracycline exposure, age >50 years, pre-existing cardiac dysfunction, and NYHA functional class II or more prior to initiation of therapy.[10,11]

Pathophysiology

Trastuzumab targets a receptor tyrosine kinase (RTK), called HER2 (also known as ErbB2 or neu), reducing its intracellular signaling ability. The ErbB family of receptor tyrosine kinases consists of cell surface proteins that regulate cell type specific functions, such as cell growth, proliferation, and survival. There are 4 types of ErbB receptors numbered "1" to "4." These receptors are stimulated by a group of proteins called neuregulins, which cause heterodimerization between ErbB2 and either ErbB4 or ErbB3.[12]

In mice with genetic defects in neuregulin-1, ErbB2, or ErbB4, the phenotype is similar, with failure of the cardiac ventricle to undergo trabeculation.[13] When the expression of ErbB2 is reduced by about 70% in mice, their hearts develop normally, but they also develop a dilated cardiomyopathy.[14] In adult rodent and human subjects, a correlation has been shown between depressed myocardial function and depressed myocardial ErbB levels.[15,16] With recovery of myocardial function, there is recovery of myocardial ErbB levels.[15] Additionally, as seen with trastuzumab, blocking ErbB2 signaling impairs myocardial function.[3] Conversely, augmentation of ErbB2 signaling has been shown to lessen rodent and dog infarct-, viral-, anthracycline- and pacing-induced models of heart failure.[17]

Neuregulin-1, through activation of ErbB2 and ErbB4, promotes hypertrophy and proliferation of adult and embryonic cardiomyocytes and, more importantly, reduces cardiomyocyte apoptosis.[18] It is felt that reduced cardiomyocyte apoptosis leads to a cycle of worsening heart failure due to a decreased number of cardiac myocytes, This causes increased mechanical stretch with neurohumoral activation and, therefore, more myocardial dysfunction and subsequent myocardial apoptosis.[19] Signaling through ErbB2 and ErbB4 protects cardiomyocytes from apoptosis by activating Akt. Akt is a serine/threonine kinase that prevents apoptosis *in vivo* by phosphorylation and inactivation of proteins involved in programmed cell death.[19,20] Activation of Akt alone is insufficient to protect cardiac myocytes from apoptosis.[21] Cardiomyocyte survival is likely the result of net cardiomyocyte signaling in favour of anti-apoptosis, with activation of other factors such as insulin-like growth factor-1, and cardiotrophin-1.[22,23]

If trastuzumab prevents apoptosis, the question then becomes: What triggers the activation of the apoptotic pathways? A '2-hit' hypothesis has been developed to explain the cardiac dysfunction that develops with trastuzumab therapy (Figure 1). Cardiac stress pathways are induced either by hemodynamic overload or anthracycline cardiotoxicity. The use of trastuzumab blocks anti-apoptotic signaling that would blunt the cardiac stress signaling pathways and, as a result, cardiac dysfunction develops.[24]

Management of patients undergoing trastuzumab therapy

Patients with pre-existing cardiac dysfunction: Since all clinical trials excluded patients with pre-existing cardiac dysfunction, it is unknown whether the use of trastuzumab worsens cardiac function. However, in the National Surgical Adjuvant Breast and Bowel Project (NSABP B-31), patients with marginal left ventricular ejection fractions (LVEFs) post-anthracycline, but who were still eligible for trastuzumab, had higher rates of

Figure 1: Mechanism of trastuzumab-related cardiotoxicity

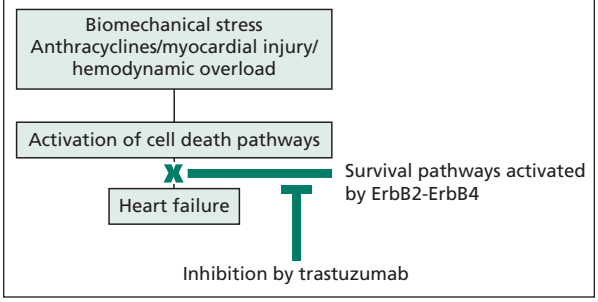

Table 2: Cardiac events with trastuzumab in early breast cancer.

Trial	Chemotherapy and trastuzumab regimen	Baseline LVEF (%)	CHF (%)	Cardiac death (n)
HERA[8]	Nil	≥ 55	0	1
	Trastuzumab x 1 yr		0.6	0
NSABP-B31[10]	Doxorubicin + cyclophosphamide then paclitaxel	≥ 50	0.8*	1
	Doxorubicin + cyclophosphamide, then paclitaxel + trastuzumab		4.1*	0
NCCTG N9831[7]	Doxorubicin + cyclophosphamide, then paclitaxel	≥ 50	0.3*	1
	Doxorubicin + cyclophosphamide, then paclitaxel then trastuzumab		2.5*	1
	Doxorubicin + cyclophosphamide, then paclitaxel + trastuzumab		3.5*	0
BCIRG 006[27]	Doxorubicin + cyclophosphamide, then docetaxel	≥ 50	0.3	0
	Doxorubicin + cyclophosphamide, then docetaxel + trastuzumab		1.6	0
	Docetaxel + carboplatin + trastuzumab		0.4	0
FinHer [9]	No trastuzumab		3	0
	Trastuzumab x 9 weeks		0	0

*Cumulative incidence

subsequent cardiac dysfunction than those who started trastuzumab with normal cardiac parameters.[7] This suggests that the presence of cardiac dysfunction should preclude the initiation of trastuzumab.

Patients who develop cardiac dysfunction: Trastuzumab-related cardiotoxicity is not dose-related and responds well to standard medical therapy for heart failure and discontinuation of trastuzumab. In a retrospective review of 173 patients treated with trastuzumab, 49 developed an asymptomatic decrease in their LVEF of <50%, a decrease of 20% below baseline in their LVEF, or signs and symptoms of CHF.[25] Of these 49 patients, 11 (79%) of 14 women who stopped trastuzumab therapy after developing symptomatic CHF, recovered with appropriate cardiac treatments. Eighty-nine percent of those with an asymptomatic decrease in their LVEF on cardiac imaging recovered with, or without, cardiac treatment after stopping trastuzumab. This recovery of LVEF is consistent with other reports.[10,26] Interestingly, there were 17 patients in this study who did not stop trastuzumab and who developed asymptomatic cardiac dysfunction; 15 recovered their LVEF, although 13 of these patients did not receive any medical therapy for their cardiac dysfunction.

Once patients have recovered from their trastuzumab-related cardiac dysfunction, the question is whether trastuzumab – a potentially life-saving therapy – can be reinitiated. The review by Guarneri et al found that of 26 patients who had full cardiac recovery and were restarted on trastuzumab, 16 (61%) had no further cardiac toxicity.[25] Of the 10 who developed recurrent cardiac toxicity, 5 had full recovery with discontinuation of trastuzumab. The long-term effect of trastuzumab on a women's risk of developing future adverse cardiac events is unknown.

Overall, evaluation of LVEF should occur prior to the initiation of trastuzumab therapy, then every 3 months during therapy, and upon completion of therapy. It should be performed more often (ie, every 4 weeks) if the LVEF is below the lower limit of normal or has decreased by at least 10% during treatment. An evaluation should also be performed should the patient develop signs and symptoms of CHF.

Minimizing cardiac dysfunction: Two strategies have been used to minimize trastuzumab-related cardiomyopathy.

The first is to avoid concurrent use of anthracyclines with trastuzumab. New regimens have been developed that integrate trastuzumab into nonanthracycline-containing regimens. The Breast Cancer International Research Group (BCIRG) 006 trial compared 2 anthracycline-containing regimens (doxorubicin and cyclophosphamide followed by paclitaxel, with or without trastuzumab) with a nonanthracycline-containing regimen (trastuzumab, docetaxel, and carboplatin). The nonanthracycline-containing regimen was reported to be as effective a treatment as anthracycline and trastuzumab-containing regimens and is associated with

a lower incidence of cardiac dysfunction.[27] Symptomatic cardiac events were 1.2% in the nonanthracycline-containing regimen, compared to 2.3% and 1.2% for the anthracycline-containing arms, with and without trastuzumab, respectively. As well, the incidence of absolute LVEF decline of >15% or below the lower limit of normal was 0.4% in the nonanthracycline-containing arm versus 2.4% and 0.6% in the anthracycline-containing arms, with and without trastuzumab.

The second strategy is to shorten the duration of therapy with trastuzumab. In the FinHer trial, following chemotherapy, HER2-positive patients were randomized to receive or not receive 9 weeks of trastuzumab.[9] The study revealed that patients receiving trastuzumab vs those not receiving trastuzumab had a better 3-year recurrence-free survival (89% vs. 78%, respectively, p=0.01) and a trend towards better overall survival (96% vs. 90%, respectively p=0.07). These outcomes with 9 weeks of trastuzumab treatment are similar to those seen in other trastuzumab trials using 1 or 2 years of treatment. Moreover, no cardiac events were seen in this trial; however; the follow-up time period was short.

Prediction and prevention

How does one identify which patients are likely to develop or are developing cardiotoxicity before left ventricular function decreases? Currently, there are no studies involving patients treated with trastuzumab. However, there are studies examining the use of troponins in cardiotoxicity from other chemotherapies such as anthracyclines. These studies have shown that troponin I levels are increased in approximately 33% of individuals after receiving high-dose chemotherapy and that this is associated with the development of reduced LVEF in the year following therapy.[28,29] Prolonged elevations in troponins are seen in patients who develop asymptomatic left ventricular dysfunction.[30]

In fact, troponin values appear to be useful in predicting the development of cardiac dysfunction. In a study of 703 cancer patients treated with high-dose chemotherapy, serial troponin I levels were measured.[31] Early troponin I levels were measured before and after each dose of chemotherapy. Late troponin I levels were measured one month after the last dose of chemotherapy. Using a positive troponin I value of > 0.08 ng/mL, patients were grouped into those:

- with negative early and late troponin I values
- with only an early increase in troponin I values
- with increased early and late values.

In the first group with negative early and late troponin I values, no significant reduction in LVEF was observed and there was only a 1% incidence of cardiac events. Whereas, in the groups where the troponin I level was elevated early or early and late, there was a greater incidence of cardiac events (37% and 84%, respectively).

Although brain natriuretic peptide (BNP) has been shown to be a predictor of anthracycline-induced cardiac dysfunction, the use of BNP or N-terminal-probrain natriuretic peptide (NT-proBNP) as a predictor of trastuzumab-related cardiotoxicity has not been extensively studied.[32] One study used NT-proBNP to examine patient hemodynamic responses to trastuzumab infusion.[33] Women with high baseline levels of NT-proBNP had increased stroke volumes, cardiac outputs, and systemic vascular resistance immediately following trastuzumab infusion. This suggests that patients with higher sympathetic activity, in parallel with higher NT-proBNP values, are at higher risk of cardiac failure. Further work is needed to clarify the role of BNP in either management or diagnosis of trastuzumab-related cardiomyopathies.

Once an at-risk patient has been identified, can the deterioration in cardiac function be prevented? Once again, there is no information regarding trastuzumab. In terms of other cardiotoxic chemotherapies, one study examined the use of angiotensin-converting enzyme inhibitors (ACEi).[34] In this study, 114 cancer patients with elevated troponin I values after receiving high-dose chemotherapy were randomized to receive, or not receive, 20 mg/d of enalapril. Enalapril was started one month after receiving high-dose chemotherapy and was continued for one year. No reductions in LVEF of >10% causing a decline below the normal limit value of 50% were observed in the treated group compared with an incidence of 43% in the untreated group. Additionally, there was only one clinical cardiac event in the enalapril group compared with 40 in the control group. This suggests that treatment with enalapril could prevent the development of late cardiotoxicity; however, the trial has been criticized for its small size and open-label design. Reproduction of the results of this study is crucial to establish ACEi as an effective preventative therapy.

Other agents, such as beta-blockers, which have proven benefits in heart failure therapy, have not been studied for the prevention and treatment of chemotherapy-induced cardiomyopathy. Dexrazoxane has been shown to prevent anthracycline cardiotoxicity, but due to the possibility that it may

decrease antitumour activity, its use has been limited.[35] Other agents that have been demonstrated to prevent anthracycline cardiotoxicity in animal models include erythropoietin, thrombopoietin, and iloprost;[36-38] however, their effect in preventing human cardiotoxicity is unknown. These agents require further study for possible roles in preventing trastuzumab-related cardiac dysfunction.

Conclusion

Trastuzumab is a life-saving therapy in the treatment of breast cancer. The use of this agent is associated with the development of systolic dysfunction in 5% of patients, with 2% developing symptomatic congestive heart failure. A "two-hit" hypothesis has been proposed for the mechanism of cardiac dysfunction: first, activation of apoptotic pathways due to anthracycline or other cardiac stress and, second, the loss of antiapoptotic signaling due to the use of trastuzumab. Trastuzumab-related cardiac dysfunction is not dose-dependent and the majority of patients recover cardiac function with discontinuation of trastuzumab and standard cardiac therapy for heart failure. Trastuzumab can be safely reinitiated once cardiac function has recovered. LVEF should be monitored during therapy. Further work is needed to elucidate the long-term cardiovascular effects of trastuzumab, identify markers that can predict which patients will develop cardiac dysfunction, and clarify the treatment options for these patients.

References

1. International Agency for Research on Cancer. *Handbooks of Cancer Prevention: Breast cancer screening*. Lyon: IARC; 2002.
2. Canadian Cancer Society/National Cancer Institute of Canada. *Canadian Cancer Statistics* 2007. Toronto, Canada; 2007.
3. Slamon DJ, Clark GM, Wong SG, et al. Human breast cancer: correlation of relapse and survival with amplification of the HER2-2/neu oncogene. *Science* 1987;235:177-182.
4. Marty M, Cognetti MM, Maraninchi D, et al. Randomized phase II trial of the efficacy and safety of trastuzumab combined with docetaxel in patients with human epidermal growth factor receptor 2-positive metastatic breast cancer administered as first-line treatment: the M77001 study group. *J Clin Oncol* 2005; 23:4265-4274.
5. Slamon DJ, Leyland-Jones B, Shak S, et al. Use of chemotherapy plus a monoclonal antibody against HER2 for metastatic breast cancer that overexpresses HER2. *N Engl J Med* 2001;344:783-792.
6. Ewer MS, Gibbs HR, Swafford J, et al. Cardiotoxicity in patients receiving trastuzumab (Herceptin): Primary toxicity, synergistic or sequential stress, or surveillance artifact? *Semin Oncol* 1999;26:96-101.
7. Romond EH, Perez EA, Bryant J, et al. Trastuzumab plus adjuvant chemotherapy for operable HER2-positive breast cancer. *N Engl J Med* 2005;353:1673-1684.
8. Piccart-Gebhart MJ, Procter M, Leyland-Jones B, et al. Trastuzumab after adjuvant chemotherapy in HER2-positive breast cancer. *N Engl J Med* 2005;353:1659-1672.
9. Joensuu H, Kellokumpu-Lehtinen PL, Bono P, et al. Adjuvant docetaxel or vinorelbine with or without trastuzumab for breast cancer. *N Engl J Med* 2006;354:809-820.
10. Tan-Chiu E, Yothers G, Romond E, et al. Assessment of cardiac dysfunction in a randomized trial comparing doxorubicin and cyclophosphamide followed by paclitaxel, with or without trastuzumab as adjuvant therapy in node-positive, human epidermal growth factor receptor 2-overexpressing breast cancer: NSABP B-31. *J Clin Oncol* 2005; 23:7811-7819.
11. Suter TM, Cook-Bruns N, Barton C. Cardiotoxicity associated with trastuzumab (Herceptin) therapy in the treatment of metastatic breast cancer. *Breast* 2004;13:173-183.
12. Freedman NJ, Ginsburg GS. Novel –and "neu" – therapeutic possibilities for heart failure. *J Am Coll Cardiol* 2006;48:1448-1450.
13. Garratt An, Oozcelik C, Birchmeier C. ErbB2 pathways in heart and neural diseases. *Trends Cardiovasc Med* 2003;13:80-86.
14. Crone SA, Zhao YY, Fan L, et al. ErbB2 is essential in the prevention of dilated cardiomyopathy. *Nat Med* 2002;8:459-65.
15. Rohrbach S, Niemann B, Silber RE, et al. Neuregulin receptors erbB2 and erbB4 in failing human myocardium –depressed expression and attenuated activation. *Basic Res Cardiol* 2002; 100:240-249.
16. Rohrbach S, Yan X, Weinberg EO, et al. Neuregulin in cardiac hypertrophy in rats with aortic stenosis. Differential expression of erbB2 and erbB4 receptors. *Circulation* 1999;100:407-412.
17. Liu X, Fu X, Li Z, et al. Neuregulin-1/erbB activation improves cardiac function and survival in models of ischemic, dilated and viral cardiomyopathy. *J Am Coll Cardiol* 2006;48:1438-1447.
18. Zhao YY, Sawyer DR, Baliga RR, et al. Neuregulins promote survival and growth of cardiac myocytes. Persistence of ErbB2 and ErbB4 expression in neonatal and adult ventricular myocytes. *J Biol Chem* 1998;273:10261-10269.
19. Foo RS, Mani K, Kitsis RN. Death begets failure in the heart. *J Clin Invest* 2005;115:565-571.
20. Yan ZZ, Tschopp O, Di-Poi N, et al. Dosage-dependent effects of Akt/protein kinase Balpha (PKBalpha) and Akt3/PKBgamma on thymus, skin and cardiovascular and nervous system development in mice. *Mol Cell Biol* 2005;25:10407-10418.
21. Skurk C, Izumiya Y, Maatz H, et al. The FOXO3a transcription factor regulated cardiac myocyte size downstream of AKT signaling. *J Biol Chem* 2005;280:20814-20823.
22. McMullen JR, Shioi T, Huang WY, et al. The insulin-like growth factor 1 receptor induces physiological heart growth via the phosphoinositide 3-kinase (P110alpha) pathway. *J Biol Chem* 2004;279:4782-4793.
23. Kuwahara K, Saito Y, Kishimoto I, et al. Cardiotrophin-1 phosphorylates akt and BAD, and prolongs cell survival via a PI3K-dependent pathway in cardiac myocytes. *J Mol Cell Cardiol* 2000;32:1385-1394.
24. Chien KR. Herceptin and the heart – a molecular modifier of cardiac failure. *N Engl J Med* 2006;354:789-790.
25. Guarneri V, Lenihan DJ, Valero V, et al. Long-term cardiac tolerability of trastuzumab in metastatic breast cancer: the MD Anderson Cancer Center experience. *J Clin Oncol* 2006;24:4107-4115.
26. Ewer MS, Vooletich MT, Durand JB, et al. Reversibility of trastuzumab-related cardiotoxicity: new insights based on clinical course and response to medical treatment. *J Clin Oncol* 2005;23:7820-7826.
27. Slamon D, Eiermann W, Robert N, et al. Phase III trial comparing AC-T with AC-TH and with TCH in the adjuvant treatment of HER2 positive early breast cancer: First planned interim efficacy analysis (abstract 1). Data presented at the 28th Annual San Antonio Breast Cancer Symposium; December 8, 2005; San Antonio, TX.
28. Cardinale D, Sandri MT, Martinoni A, et al. Left ventricular dysfunction predicted by early troponin I release after high-dose chemotherapy. *J Am Coll Cardiol* 2000;34:517-522.
29. Cardinale D, Sandri MT, Martinoni A, et al. Myocardial injury revealed by plasma troponin I in breast cancer treated with high-dose chemotherapy. *Ann Oncol* 2002;13:710-715.
30. Auner HW, Tinchon C, Linkesch W, et al. Prolonged monitoring of troponin T for detection of anthracycline cardiotoxicity in adults with hematologic malignancies. *Coron Artery Dis* 1997;8:537-541.

31. Cardinale D, Sandri MT, Colombo A, et al. Prognostic value of troponin I in cardiac risk stratification of cancer patients undergoing high-dose chemotherapy. *Circulation* 2004;109:2749-2754.
32. Okumura H, Iuchi K, Yoshida T, et al. Brain natriuretic peptide is a predictor of anthracycline-induced cardiotoxicity. *Acta Haematol* 2000;103:158-163.
33. Knobloch K, Tepe J, Lichtinghagen R, et al. Simultaneous hemodynamic and serological cardiotoxicity during immunotherapy with trastuzumab. *Int J Cardiol* 2007; (e-published Mar 30).
34. Carinale D, Colombo A, Sandri MT, et al. Prevention of high-dose chemotherapy-induced cardiotoxicity in high-risk patients by angiotensin-converting enzyme inhibition. *Circulation* 2006;113:2474-2481.
35. van Dalen E, Michiels E, Caron H, et al. Different anthracycline derivates for reducing cardiotoxicity in cancer patients. *Cochrane Database Syst Rev* 2006:4:CD0005006.
36. Li L, Takemura G, Li Y, et al. Preventive effect of erythropoietin on cardiac dysfunction in doxorubicin-induced cardiomyopathy. *Circulation* 2006;113:535-543.
37. Li K, Sung RY, Huang WZ, et al. Thrombopoietin protects against in vitro and in vivo cardiotoxicity induced by doxorubicin. *Circulation* 2006;113:2211-2220.
38. Neilan TG, Jassal DS, Scully MF, et al. Iloprost attenuates doxorubicin-induced cardiac injury in a murine model without compromising tumour suppression. *Eur Heart J* 2006;27:1251-1256.

Abstracts of Interest

Prognostic Value of Troponin I in Cardiac Risk Stratification of Cancer Patients Undergoing High-Dose Chemotherapy

CARDINALE D, SANDRI MT, COLOMBO A, COLOMBO N, BOERI M, LAMANTIA G, CIVELLI M, PECCATORI F, MARTINELLI G, FIORENTINI C, CIPOLLA CM. MILAN, ITALY

BACKGROUND: In patients with aggressive malignancies who are undergoing high-dose chemotherapy, even minimal elevation of troponin I (TnI) is associated with late left ventricular dysfunction. The time course of the subclinical myocardial damage and its impact on the clinical outcome have never been investigated previously.

METHODS AND RESULTS: In 703 cancer patients, we measured TnI soon after chemotherapy (early TnI) and 1 month later (late TnI). Troponin was considered positive for values ≥ 0.08 ng/mL. Clinical and left ventricular ejection fraction evaluation (echocardiography) were performed before chemotherapy, 1, 3, 6, and 12 months after the end of the treatment, and again every 6 months afterward. Three different TnI patterns were identified, and patients were grouped accordingly. In 495 patients, both early and late TnI values were < 0.08 ng/mL (TnI -/- group); in 145, there was only an early increase (TnI +/- group); and in 63 patients, both values increased (TnI +/+ group). In the TnI -/-group, no significant reduction in ejection fraction was observed during the follow-up, and there was a very low incidence of cardiac events (1%). In contrast, a greater incidence of cardiac events occurred in TnI-positive patients, particularly in the TnI +/+ group (84% versus 37% in the TnI +/- group; P < 0.001).

CONCLUSIONS: TnI release pattern after high-dose chemotherapy identifies patients at different risks of cardiac events in the 3 years thereafter. This stratification allows us to differentiate the monitoring program and to plan, in selected patients, preventive strategies aimed at improving clinical outcome.

Circulation 2004;109:2749-2754.

Cardiac Dysfunction in the Trastuzumab Clinical Trials Experience

SEIDMAN A, HUDIS C, PIERRI MK, SHAK S, PATON V, ASHBY M, MURPHY M, STEWART SJ, KEEFE D. NEW YORK, NY

PURPOSE: This study sought to estimate cardiac dysfunction (CD) risk for patients receiving trastuzumab; to characterize observed CD by severity, treatment, and clinical outcome; to assess effects of baseline clinical risk factors on CD; and to assess effects of cumulative doses of anthracyclines and trastuzumab on CD.

PATIENTS AND METHODS: A retrospective review of records for patients enrolled onto any of seven phase II and III trastuzumab clinical trials was performed. Predefined criteria were used for the diagnosis, and the New York Heart Association functional classification systemwas used to document CD severity. Product-limit estimates were used to summarize the cumulative anthracycline and trastuzumab doses at the time of CD onset.

RESULTS: Patients treated with trastuzumab were found to be at an increased risk for CD. The incidence zumab and anthracycline plus cyclophosphamide (27%). The risk was substantially lower in patients receiving paclitaxel and trastuzumab (13%) or trastuzumab alone (3% to 7%); however, most of these patients had received prior anthracycline therapy. CD was noted in 8% of patients receiving anthracycline plus cyclophosphamide and 1% receiving paclitaxel alone. Most trastuzumab-treated patients developing CD were symptomatic (75%), and most improved with standard treatment for congestive heart failure (79%).

CONCLUSION: Trastuzumab is associated with an increased risk of CD, which is greatest in patients receiving concurrent anthracyclines. In most patients with metastatic breast cancer, the risk of CD can be justified given the improvement in overall survival previously reported with trastuzumab.

J Clin Oncol 2002;20:1215-1221.

Upcoming meetings

1-5 September 2007
European Society of Cardiology Annual Meeting
Vienna, Austria
Contact: www.escardio.org

20-24 October 2007
Canadian Cardiovascular Society CCC 2007
Quebec City, Quebec
Contact: www.cardiocongress.org

Disclosure Statement: *Dr. Moe and Dr. Tsng have declared that they have no disclosures to announce in association with the contents of this issue.*

Change of address notices and requests for subscriptions to *Cardiology Rounds* are to be sent by mail to P.O. Box 310, Station H, Montreal, Quebec H3G 2K8 or by fax to (514) 932-5114 or by e-mail to info@snellmedical.com. Please reference *Cardiology Rounds* in your correspondence. Undeliverable copies are to be sent to the address above. Publications Post #40032303

This publication is made possible by an educational grant from

Novartis Pharmaceuticals Canada Inc.