

CARDIAC MONITORING IN HER-2 POSITIVE ELDERLY PATIENTS TREATED WITH TRANSTUZUMAB

An Article Review By **Dr. Rajani Sinha, India**
(MBBS, MMSc in Oncology Student of Texila American University)
Email:- dr.rajanisinha@yahoo.com

SOURCE

Reviewing the article “Transtuzumab related cardiotoxicity in the elderly : a role for cardiovascular risk factor.” C. Serrano, J Cortes, L.De Mattos Arruda, M. Bellet, P. Gomez, C. Saura, J. Perez, M. Vidal, E. Munoz – Couselo, M.J. Carreras, G. Sanchez-Olle, J. Taberero, J. Baselga & S. Di Cosimo.

KEYWORDS

Cardiotoxicity, Transtuzumab, HER -2 over expression, Breast Cancer, Elderly

INTRODUCTION

Human epidermal growth factor receptor -2 (HER-2) is a member of EGFR (epidermal growth factor receptor) family, plays a very significant role in cell growth and proliferation [1] HER – 2 protein is over expressed in 20% of breast cancer and is associated within aggressive course , poor prognosis and response to treatment [2-3]. The introduction of transtuzumab, a monoclonal antibody directed against, the extra cellular domain of HER - 2 receptor, has revolutionized the treatment of HER – 2 positive early breast cancer and has led to significant improvement in disease free survival and overall survival over chemotherapy alone.

In randomized multicenter trials with HER – 2 over expressing metastatic breast cancer patients, addition of transtuzumab to first line chemotherapy has improved objective response rate, the time to disease progression and overall survival over chemotherapy alone [4,5]. Hence transtummab is now considered as the standard of care for all patients who over amplify HER – 2 neu receptors.

These benefits have come with the cost of increased risk of cardiotoxicity. Trastuzumab related cardiotoxicity is mediated by interruption of normal HER – 2 signaling pathway in the heart, which is responsible for maintenance of normal growth, repair and survival of cardiomyocytes. Cardiotoxicity related to trastuzumab is different from that of anthracyclins as it is not dose related and appears to be largely reversible on discontinuation of therapy. There is no alteration in ultra structural abnormalities whereas that due to anthracyclins are caused by free radical induced oxidative stress to cardiac muscle cells [12].

REVIEW OF LITERATURE

In the pivotal metastatic Breast Cancer trials cardiac dysfunction was seen in the patient treated with trastuzumab and chemotherapy. The incidence was greatest among the patients who received concurrent anthracyclins. The findings led to design the subsequent trastuzumab trials which included prospective monitoring of cardiac effects and protocols for its management. The risk of cardiotoxicity also driven efforts to develop non- anthracyclin based regimens for HER – 2 positive breast cancer patients.

Four major adjuvant trials: HERA (herceptin adjuvant trial), NSABP-B31 trial, the national surgical adjuvant breast and bowel project,(N CCTG) N 9831 trial, the North Central Cancer Treatment Group and (BCIRG) 006 trial, the Breast Cancer International Research Group – investigated various adjuvant approaches with trastuzumab. More than 13000 women enrolled were HER-2 positive. Results indicated that adjuvant trastuzumab reduces recurrence by nearly 50% and increases overall survival by 33% therefore; trastuzumab is adopted as the standard for care in early breast cancer.

Comparisons between studies related to cardiotoxicity are difficult as they used different criteria for assessing cardiac function. The rate of asymptomatic decline by more than 10% in LVEF ranged from a high of 18% in BCIRG 006, to a low of 3% in HERA.

In HERA incidence of cardiotoxicities were higher in trastuzumab group and more in patients who were treated with cumulative doses of doxorubicin (287 mg/m² vs 257 mg/m² or epirubicin (480 mg/m² Vs 422 mg/m²) and had lower baseline LVEF (55% - 60% Vs. \geq 60% and 60% - 65% Vs \geq 65%).

No association was found between cardiac end points and older age, previous cardiac disease, hyperlipidemia or hypertension.

The Finland Herceptin trial (Fin HER) ,HER -2positive patients who received 9 weeks of trastuzumab infusion showed better rate of 3 years recurrence free survival that the women who do not. No decrease in LVEF or Cardiac failure was observed.

BRIEF REVIEW OF ARTICLES

(1) Reversibility of Trastuzumab– Related Cardiotoxicity: New Insights Based on Clinical Course and Response to Medical Treatment. Michael S.Ewer et al [6] studied on the patients who developed cardiotoxicity while receiving trastuzumab and they improved on discontinuation of the drug (suggesting its reversible action on cardiac myocytes).The found that the mechanism underlying trastuzumab related cardiotoxicity are different from anthracyclins, in part due to absence of ultrastructural changes (evident on endomyocardial biopsy).Mean recovery time of LVEF was 1.5 months and most of the patients could resume the treatment.

(2) Heart Remodeling induced by adjuvant trastuzumab– Containing chemotherapy for breast cancer over expressing human epidermal growth factor receptor type – 2. Prospective study by Piotrowski G et al.[7] . They investigated the cardiac changes that occurred in patients of HER -2 positive breast cancer who received trastuzumab in adjuvant setting and concluded that trastuzumab induces left ventricular and left atrial cavity dilatation together with LV systolic function impairment.

(3) Trastuzumab related cardiac events in the treatment of Early Breast Cancer. Fried G, Regev T ,Moskovitz M.. [8].

A retrospective study was performed on the patients of cancer breast HER – 2 positive who received trastuzumab, cardiac events (CE) were observed in 21% patients. There was a significant decrease in LVEF between baseline/ post AC and during trastuzumab treatment (mean LVEF 64.29% vs 61.97%, $P < 0.001$). Treatment related risk factors were age and interval since last AC. Trastuzumab loading dose did not influence CE rates. Patients who received left chest wall irradiation had significantly increased CE rates vs patients without radiotherapy ($p < 0.05$). Any cardio vascular risk factor caused increased risk though not statistically significant.

Concluded that age and prior Anthracyclins appeared to predict the cardiotoxic event hence cardiac monitoring seems important for all patients during treatment with trastuzumab especially in elderly.

(4) Adjuvant trastuzumab cardiotoxicity in patients over 60years of age with early breast cancer, a multicentric cohort analysis. [10]

L.Tarantini et al analysed 499 HER 2 +ve early breast cancer patients who were treated with adjuvant trastuzumab and chemotherapy at 10 Italian institutions. They evaluated disease prevalence and patient characteristics in patients over 60 years of age and prevalence of trastuzumab and chemotherapy cardio toxicity and risk factors. They concluded that 32% of HER 2 positive EBC patients treated with trastuzumab chemotherapy are 'over 60'. These patients have increased cardiovascular risk profile and develop a trastuzumab chemotherapy cardiotoxicity commonly.

(5)Early increases in multiple Biomarkers Predict Subsequent cardiotoxicity in Breast Cancer patients treated with Doxorubicin, Taxanes and trastuzumab. by Ky B et al.

They found that early increases in Troponin I and MPO (myelo-peroxidase) offer additive information about cardio toxicity risk in patients undergoing doxorubicin and trastuzumab therapy.

ARTICLE SUMMARY

The article states that they reviewed the records of elderly breast cancer patients ≥ 70 years of age who were treated with trastuzumab since 2006. NYHA classification was used to define symptomatic cardiotoxicity.[25] Asymptomatic cardiotoxicity was defined as an absolute drop of LVEF by $\geq 20\%$ or a drop of $\geq 10\%$ with final LVEF $< 50\%$. They studied 45 patients of median age 75.9 years, of them, 12.5% patients of early breast cancer and 23.8% patients with advanced disease experienced asymptomatic cardiotoxicity. 8.9% patients developed symptomatic congestive heart failure were all with advanced breast cancer. All the patients except one recovered in a median time of 5 weeks . They concluded that elderly breast cancer patients treated with trastuzumab have an increased incidence of cardiotoxicities as they have history of cardiac disease and/or diabetes. They have advised for continuous cardiac monitoring in this group of patients.

ARTICLE STRUCTURE

The article is well written. It has short paragraphs with bold headings. This makes it easy to comprehend.

The article starts with an abstract which tells us in nutshell the subject and the outcome of the study. It also tells us the background behind the study. It has an introduction which sites the brief concept of HER-2 receptor and trastuzumab. The mechanism of action of trastuzumab induced cardiotoxicity is due to blockade of HER – 2 signaling which is responsible for growth, repair

and survival of cardio myocytes [12]. A large review of advanced breast cancer patients showed increased risk of cardiac events in patients receiving concomitant trastuzumab and anthracyllin derivative plus cyclophosphamide ~ 27% and a substantially lower risk in patients treated with paclitaxel and trastuzumab ~ 13% or with trastuzumab alone ~ 3-7%. Other major risk factors for trastuzumab related cardiotoxicity is age > 60 years, lower baseline LVEF [4, 14] and prior anthracycline exposure.

Next paragraph describes about patients and methods. It says detail about the patients inclusion criteria and exclusion criteria. Definition of cardiotoxicity assessment is clear LVEF assessed either by MUGA scan or by echocardiography [16]. Cardiac events were classified according to NYHA system to document symptomatic CE. [17] Definition of asymptomatic cardiotoxicity is clear.

Results of the retrospective study is described in detail. 26.7% of patients experienced cardiac events. 17.8% developed asymptomatic LVEF decline and 8.9% developed symptomatic congestive heart failure (CHF). All the patients recovered completely after discontinuation of trastuzumab over a median time of 6 weeks. After reversal of LVEF, treatment was restarted with trastuzumab. Only one patient had repeat asymptomatic fall in LVEF which completely recovered without discontinuation of the drug.

All the patients with symptomatic CHF presented with rapidly progressive (<_ 10 days) dyspnoea and orthopnea. Echocardiography, 2 D ECHO and chest X-ray were used to diagnose CHF. Patients presenting with cardiac events (symptomatic or asymptomatic) were more often had cardiovascular risk factors. They also were associated with overweight BMI > 30 (P = 0.045), history of previous cardiac event (P = 0.047) and diabetes mellitus (P = 0.017).

This was followed by discussion and conclusion. In all the breast cancer patients who over express HER – 2 neu receptors, trastuzumab is the standard of care [18,19]. Since incidence of cancer is increasing with age and nearly 70% of newly diagnosed cancer are > 65 years of age [20], elderly cancer patients are expected to increase in the coming years. So, the information of efficacy and safety of anticancer treatment is needed especially in this subgroup of patients who are mostly excluded from pivotal studies. [15, 21] Hence, this study aimed to assess cardiac safety profile and potential cardiac risk factors associated with trastuzumab treatment in patients > 70 years.

The study showed that overall incidence of cardiac events ~26.7% and symptomatic CE in 8.9% cases. Most of the cases(91.7%) are reversible. The results were slightly higher than that reported in trastuzumab pivotal trials [4,5]. This discordance is due to the characteristics of patient population- age and comorbidities. Authors said that their findings were more consistent with that from M D Anderson Cancer Centre than those from pivotal studies.

Authors concluded that there is significant increase in incidence of cardiac events in those patients who had history of cardiac disease &/ or diabetes. Hypertension and smoking history were not demonstrated to increase trastuzumab related cardiotoxicity. Trastuzumab safety profile among elderly breast cancer patients are similar to already reported in earlier studies [13], high proportion of reversibility and safety on retreatment [14, 6] and lack of association between trastuzumab dose [14] and left sided radiotherapy [22] and cardiotoxicity.

Authors also mentioned that there is need for close surveillance of early symptoms and cardiac function in elderly breast cancer patients treated with trastuzumab and to refer them to cardiologist if one or more cardiovascular risk factors are present before or during the treatment with trastuzumab for careful monitoring by multidisciplinary team .

The style of writing is concise and fluid. It serves the purpose of transferring basic aim of study and suggests that further prospective clinical trial are awaited to have more cardiac safety data in elderly population. It also suggest that troponin I level might help to establish diagnosis and prognosis in such patients [24,25].

The article is supported by well documented and acclaimed references.

ARTICLE CRITIQUE

AUTHORITY

The authors are from Breast Cancer Centre, Department of Medical Oncology Vall d' Hebron University Hospital Barcelona, Spain. The lead author C. Secrano is heading the department. The co-authors are working in the same faculty.

ACCURACY

The authors have tried to be accurate. They have referred to relevant articles published in various journals like New England Journal, Journal of Clinical Oncology. These articles throw light on the main side effect of trastuzumab - cardiotoxicity – rate of incidence, mechanism of action and reversibility on discontinuation of the drug, so this article is accurate. It is unique in the sense that it has studied cardiotoxicity related to trastuzumab in elderly population which are usually underrepresented in most of the clinical trials. Moreover it will also stimulate more clinical trials to include such patients based on their conclusions which will prove accuracy of the study in a prospective way.

CURRENCY

The article is current as there has been no similar study in the past. There has been multiple studies in younger patients which highlights the cardiotoxic effects of trastuzumab and its reversible action.

RELEVANCE

The article is relevant because the incidence of cancer is greatly increasing with age and almost 70% of newly diagnosed cancer patients are in age group >65 years [20] so the study is very much relevant as it has focused on the cardiotoxicity related to trastuzumab treatment in the elderly patients who mostly have one or more cardiovascular risk factors.

OBJECTIVITY

The information in this article has been taken with the objective to analyse the risk of cardiac events in relation to treatment with trastuzumab in elderly breast cancer patients who generally are predisposed with one or more cardiovascular risk factors.

STABILITY

The fact that this article is published in the Annals of Oncology speaks by itself the stability of the article.

ANALYSIS OF GRAPH / IMAGE / TABLE

Table 1- gives details of patient demographics- number of patients in various age subgroups, ECOG performance states, stage of the disease, histological type and their baseline LVEF.

Table 2 - shows details of LVEF variation (symptomatic or asymptomatic) cardiac events distributed by stage of the disease per patients.

Table 3 – gives univariate and multivariate analysis of Cardiac Risk Factors (CRF). Comprehensive analysis of CRF and trastuzumab related cardiac toxicity in an elderly breast cancer population suggest a significant increase in incidence of CE among patients with a history of cardiac disease and diabetes. Other factors like hypertension and smoking history do not relate to increase in cardiotoxicity though the data interpreted is by a small sample size.

RECENT ADVANCES RELATED TO THE TOPIC

Data obtained from this study can serve to advise clinicians to be cautious while administering trastuzumab in elderly, Her-2 positive breast cancer patients especially when they have one or more CRF. It is the first kind of its study that may stimulate further prospective studies involving elderly patients to prove more accurate data with respect to trastuzumab related cardiotoxicity.

CONCLUSION

Trastuzumab can be safely administered in elderly patients with strict surveillance and monitoring of LVEF before and during trastuzumab treatment. The fact that mortality rate at 5 years after diagnosis of CHF is ~ 50% in patients > 65 years [23], it is necessary to monitor early symptoms and cardiac function in trastuzumab treated elderly patients. Hence, can be referred to cardiologist for prompt management of early symptoms in such patients

REFERENCES

- 1) Balducci L, Exlermann M. Cancer and aging. An evolving Panorama. Hematol Oncol Clin North Am 2000; 14: 1 – 16.
- 2) Cardinale D, Colombo A, Torrissi R et al. Trastuzumab induced cardiotoxicity: Clinical and Prognostic implications of troponin I evaluation J Clin Oncol 2010; 28: 3910-3916.
- 3) Cardinale D, Sandri MT. Role of Biomarkers in Chemotherapy induced cardio toxicity Prog Cardiovasc. Dis 2010; 53: 121 – 129.
- 4) Carlson RW, Allred DC, Anderson BO et al. Breast Cancer Clinical practice guidelines in oncology J Natl Compr Cane Netw 2009; 7: 122-192.
- 5) 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 Clinoncol 2005;23:7820-7826.
- 6) Force T, Krause DS, Van Etten A. Molecular mechanisms of cardio toxicity of tyrosine kinase inhibition. Nat Rev Cancer 2007; 7: 332-344.
- 7) Fried G, Regev T, Moskowitz M.. Trastuzumab related cardiac events in the treatment of Early breast cancer.

- 8) Goldhirsch A, Ingle JN, Gelber RD et al. Thresholds for therapies: highlights of St Gallen International Expert consensus on primary therapy of early breast cancer 2009. *Ann Oncol* 2009; 20: 1319-1329.
- 9) Guarneri V, Lenihan DJ, Valero V et al. Long term cardiac tolerability of trastuzumab in metastatic breast cancer. The M.D. Anderson Cancer Center Experience *J Clin Oncol* 2006; 24: 4107 – 4115
- 10) Halyard MY, Pisanoky TM, Ducek AC et al. Radiotherapy and adjuvant trastuzumab in operable breast cancer, tolerability and adverse event data from the NCCTG phase III trial N 9831. *J Clin Oncol* 2009; 27: 2638 – 2644.
- 11) Hunt SA. ACC/AHA 2005 guideline update for the diagnosis and management of chronic heart failure in the adult: a report of American College of Cardiology/American Heart Association Task Force on Practice Guidelines (writing committee to update the 2001 Guidelines for the Evaluation and Management of Heart Failure) *J. Am Coll Cardiol* 2005; 4b: e1 – e 82.
- 12) Hutchins LF, Unger JM, Crowley J J et al. Underrepresentation of patients 65 years of age or older in cancer- treatment trials. *N Engl J Med* 1999; 341: 2061-2067
- 13) Ky B, Putt M, Sawaya H, French B, Januzzi JL, Sebag IA, Plana JC, Cohen V, Banchs J, Carver JR, Wieggers SE, Martin RP, Picard MH, Gerszten RE, Halpern EF, Passeri J, Kuter I, Scherrer-Crosbie M.. Early increases in multiple Biomarkers Predict Subsequent cardiotoxicity in Breast Cancer patients treated with Doxorubicin, Taxanes and trastuzumab
- 14) L.Tarantini, S.Gori, P.Faggiano et al. Adjuvant trastuzumab cardiotoxicity in patients over 60 yrs of age with early breast cancer: a multicentric cohort study. *Annals of oncology* Vol 23 no 12 Dec. 2012
- 15) Levy D, Kenchaiah S, Larson MG et al. Longterm trends in the incidence of and survival with heart failure. *N Eng J med* 2002; 347: 1397 – 1402.
- 16) Marty M, Cognetti F, Maraninchi D et al. Randomised phase II trial of efficacy and safety of trastuzumab combined with docetaxel in patients with her-2 positive metastatic breast cancer administered as first line treatment: the M77001 study group. *JCO* 2005.
- 17) Naumann D, Rusius V, Margiotta C, Nevill A, Carmichael A, Rea D, Sintler M. Factors predicting trastuzumab – related cardiotoxicity in a real world population of women with HER 2 + breast cancer .
- 18) New York Heart Association Nomenclature and Criteria for Diagnosis of Disease of Heart and Great Vessels. 7.th edition Boston, MA: Little Brown 1973.

- 19) Palk S, Hazan R, Fisher ER et al. Pathologic findings from NSABP JCO 1990.
- 20) Perez EA, Rodoheffer R. Clinical Cardiac tolerability of trastuzumab J clin Oncol 2004; 22; 322 – 329.
- 21) Piotrowski G, Gawor R, Bourge RC, Stasiak A, Potemski P, Gawor Z, Nanda NC, Banach M. Heart Remodeling induced by adjuvant trastuzumab – Containing chemotherapy for breast cancer overexpressing human epidermal growth factor receptor type – 2.
- 22) Salmon DJ, Clark GM, Wong SG et al. Human breast cancer correlation of relapse and survival with amplification of HER – 2/neu oncogene. Science 1987;235:177-182.
- 23) Salmon DJ, Leyland-Jones B, Shak S et al. Use of chemotherapy plus a monoclonal antibody against HER-2 for metastatic breast cancer that overexpress HER-2. N Engl J med 2001;344:783-792.
- 24) Slamon D.J, Godolphin W, Jones LA et al studies of HER – 2/neu proto oncogene in human breast and ovarian cancer Science 1989.;244:707-712
- 25) Yancik R, Wesley MN, Ries et al. Effect of age and comorbidity in post menopausal breast cancer patients aged 55 years and older JAMA 2001; 285: 885-892.