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TIMING OF TRASTUZUMAB AND RISK OF CARDIAC DYSFUNCTION IN HER2 POSITIVE EARLY BREAST CANCER PATIENTS

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Summary

Breast cancer is the most common malignant tumor in females in the world. Age is significant risk factor and incidence increases rapidly after age of 35. Approximately one fourth of patients with breast cancer have tumors that overexpress HER2 protein or amplify the HER2/neu gene.Trastuzumab is a recombinant humanized monoclonal antibody that binds to a specific extracellular growth factor, human epidermal growth factor type 2 HER 2-neu or ErbB2, tyrosine kinase receptor responsible for alterations in cellular metabolism and growth.Clinical studies have shown that trastuzumab given concurrently or following adjuvant chemotherapy improves disease-free survival (DFS) and overal survival (OS) in early-stage HER-2 positive breast cancer. HERA study (Herceptin in Adjuvant breast cancer) showed that one of fifty women treated with trastuzumab adjuvantly developes congestive heart failure during treatment.Mechanisms of trastuzumab induced cardiac dysfunction are not clear yet.Studies have shown that differences in timing of trastuzumab after chemotherapy and differences in total dose of anthracyclines can explain differences in incidence of cardiac dysfunction. The aim of our study was to determine incidence of trastuzumab induced cardiac dysfunction in patients with HER2 positive early breast cancer and impact of time interval between administration of chemotherapy and trastuzumab on prevalence of cardiac dysfunction. Follow up included 140 patients with early HER2 positive breast cancer treated with trastuzumab adjuvantly. Seventeen patients developed symptomatic cardiac dysfunction (12.1%) of which 6 developed severe congestive heart failure NYHA III/IV(4.2%) and 11 moderate NYHA II/III (7.9%).Patients who started trastuzumab therapy 11 to 20 days after finishing chemotherapy had 11% incidence of symptomatic heart failure, same as those patients who started trastuzumab 26 to 35 days after chemotherapy. There were no cardiac events if treatment was started 35 days after chemotherapy. Highest incidence of congestive heart failure was registered when trastuzumab was applied 21 to 25 days after adjuvant chemotherapy (22%). Time interval between cessation of adjuvant chemotherapy and first trastuzumab application has a significant impact on prevalence of trastuzumab induced cardiac dysfunction.

KEY WORDS: *breast cancer, trastuzumab, cardiac dysfunction, adjuvant chemotherapy, anthracyclines*

VRIJEME PRIMJENE TRASTUZUMABA I RIZIK ZA RAZVOJ SRČANE DISFUNKCIJE U BOLESNICA SA RANIM HER2 POZITIVNIM KARCINOMOM DOJKE

Sažetak

Karcinom je najčešći maligni tumor u žena u svijetu. Dob je značajan rizični faktor i incidencija se povećava iznad dobi od 35 godina. Otprilike četvrtina bolesnica oboljelih od raka dojke ima tumor koji prekomjerno izražava HER2. Trastuzumab je rekombinantno humanizirano monoklonalno protutijelo koje se veže na humani epidermalni faktor rasta tip 2 HER2-neu ili ErbB2, tirozin kinazni receptor odgovoran za promjene u metabolizmu i rastu stanice. Kliničke studije su pokazale da davanje trastuzumaba konkomitantno s ili nakon adjuvantne kemoterapije produžuje period bez povrata bolesti (DSF) i ukupno preživljenje (OS) u ranog HER2 pozitivnog karcinoma dojke. Studija HERA (Herceptin in Adjuvant Breast Cancer) je pokazala da jedna od pedeset žena liječenih trastuzumabom adjuvantno, razvija kongestivno zatajenje srca

tijekom liječenja. Mehanizmi nastanka trastuzumabom inducirane kardiotoksičnosti još nisu potpuno razjašnjeni. Studije su pokazale da razlike u vremenu započimanja terapije trastuzumabom nakon završene adjuvantne kemoterapije i razlike u ukupnoj dozi antraciklina mogu objasniti razlike u incidenciji srčanog zatajenja. Cilj našeg istraživanja je bio odrediti incidenciju trastuzumabom inducirane kardiotoksičnosti u bolesnica s ranim HER2 pozitivnim karcinomom dojke te odrediti utjecaj vremenskog intervala od završetka kemoterapije do početka liječenja trastuzumabom na pojavnost srčanog zatajenja. Praćenje je uključilo 140 bolesnica s ranim HER2 pozitivnim karcinomom dojke koje su liječenje trastuzumabom adjuvantno. 17 bolesnica je razvilo simptomatsko srčano zatajenje (12.1%) od kojih 6 teškog stupnja NYHA III/IV(4.2%) a 11 umjerenog NYHA II/III (7.9%).Bolesnice koje su započele liječenje trastuzumabom 11 do 20 dana po završetku kemoterapije su imale incidenciju simptomatskog srčanog zatajenja 11%, kao i bolesnice koje su započele terapiju trastuzumabom 26 do 35 dana nakon kemoterapije. U bolesnica koje su liječenje započele 35 dana nakon kemoterapije nije zabilježeno kardijalnih događanja. Najviša incidencija kongestivnog zatajenja srca je zabilježena kada je terapija trastuzumabom započeta 21 do 25 dana nakon adjuvantne kemoterapije (22%). Vremenski interval između završetka adjuvantne kemoterapije i prve aplikacije trastuzumaba ima značajan utjecaj na pojavnost trastuzumabom induciranog srčanog zatajenja.

KLJUČNE RIJEČI: *karcinom dojke, trastuzumab, srčano zatajenje, adjuvantna kemoterapija, antraciklini*

INTRODUCTION

Breast cancer is the most common malignant tumor in females in the world. It affects 10-12% of female population with 1.2 million of newly diagnosed cases per year and 500 000 deaths per year. Age is significant risk factor and incidence increases rapidly after age of 35(1). According to Croatian National cancer register, breast cancer is the most common cancer among women. In 2008, 2473 women were diagnosed with breast cancer and in 2009 902 women died from it. Statistically breast cancer is the most common cause of death from malignant disease in Croatia(2). Approximately 1/4 of patients with breast cancer have tumors that overexpress the HER2 protein or amplify the HER2/neu gene. These HER-2 positive tumors are associated with more aggressive clinical course than HER-2 negative tumors (3).

Trastuzumab is a recombinant humanized monoclonal antibody that binds to a specific extracellular growth factor, human epidermal growth factor type 2 HER 2-neu or ErbB2, tyrosine kinase receptor responsible for alterations in cellular metabolism and growth. Trastuzumab was approved by the Food and Drug Administration (FDA) in 1998 for the treatment of advanced breast carcinoma overexpressing HER-2 oncogene and in 2006 for HER-2 positive early breast cancer (4,5).

Clinical studies have shown that trastuzumab given concurrently or following adjuvant chemotherapy improved disease-free survival (DFS) and overal survival (OS) in early-stage HER-2 positive breast cancer (6,7) (Table 1).

Table 1.

CARDIOTOXICITY IN ADJUVANT TRASTUZUMAB TRIALS (CHF-CLINICAL CONGESTIVE HEART FAILURE; LVEF-LEFT VENTRICULAR EJECTION FRACTION; HERA-HERCEPTIN ADJUVANT TRIALS; NCCTG-NORTH CENTRAL CANCER TREATMENT GROUP; NSABP-NATIONAL SURGICAL ADJUVANT BREAST AND BOWEL PROJECT; BCIRG-BREAST CANCER INTERNATIONAL RESEARCH GROUP)

Trial	Cardiac death	Severe CHF (%)	Simptomatic CHF (%)	Asymtomatic drop in LVEF (%)
HERA	0	0.6	2.1	7.4
NSABP-31	0	4.1	5.1	14
NCCTG-9831	1	3.3	N/A	10.8
BCIRG-006	0	1.6	1.7	17.3
FinHer	0	0	N/A	3.5

HERA study (Herceptin in Adjuvant breast cancer) showed that one of fifty women treated with trastuzumab adjuvantly developes congestive heart failure during treatment (7).

Mechanismsof trastuzumab induced cardiac dysfunction are not clear yet. Blocking of neuregulin 1β/ErbB signal pathway in heart is considered one of the possible mechanisms (8,9). Unlike anthracycline induced cardiotoxicity, trastuzumab induced cardiac dysfunction is dose independent, there is no cumulative dose, there is no structural damage of cardiomyocytes, there is no cell necrosis and it is often completely reversible (10–15).

Studies have shown that differences in timing of trastuzumab after chemotherapy and differences in total dose of anthracyclines can explain differences in incidence of cardiac dysfunction (6).

In patients simultaneously treated with anthracyclines and trastuzumab the probability of cardiotoxicity development increased after a cumulative dose of doxorubicin of>300 mg/2. The sequence in which chemotherapy agents are administered seem to influence the development of cardiac dysfunction. When anthracyclines and trastuzumab are administered simultaneously, the incidence of NYHA class III or IV congestive heart failure (CHF) is 16%. The interval between administration of anthracycline and trastuzumab was about 3 weeks in the NSABP B-31 and BCIRG 006 trials, and it showed an incidence of class III or IV CHF of 4.1% and 1.6%, respectively. This interval was larger in HERA trial, being approximately 3 months, and incidence of cardiac dysfunction was 0.6%, similar to the number obtained in the non-anthracycline arm of the BCIRG 006 trial (0.4%). It seems that the greater the interval between these two drugs, the less cardiotoxicity is found (15,16) (Figure 1).

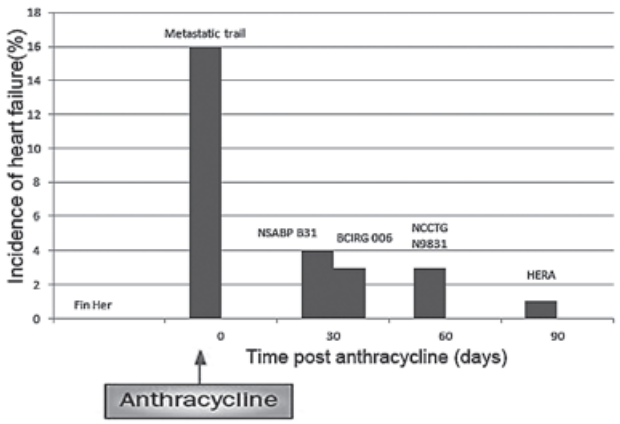

Figure 1. Incidence of heart failure in the different trials regarding time post anthracycline treatment

Trastuzumab significantly increased the risk of CHF in patients receiving anthracycline-based chemotherapy, but not in patients receiving non-anthracycline chemotherapy. (17)

Trastuzumab is golden standard tor treatment of early and metastatic HER2 positive breast cancer but patients should be closely monitored for cardiac dysfunction. Survival of severe CHF can be compared with survival of metastatic breast cancer. 5-year survival of severe CHF isapproximately 50%, while survival of breast cancer with positive axillary lymph nodes is 77% (4).

AIM

To determine incidence of trastuzumab induced cardiac dysfunction in patients with HER2 positive early breast cancer and impact of time interval between administration of chemotherapy and trastuzumab on prevalence of cardiac dysfunction.

MATERIAL AND METHODS

The study included patients treated with adjuvant trastuzumab in period from January 1st 2007 to December 31st 2008. Median follow up period was 22 months (9-32 months). All of the patients received prior anthracycline based adjuvant chemotherapy: 65% AC protocol (Adriamycin 60 mg/m^2, Cyclophosphamid 600 mg/m^2) 6 cycles every three weeks; 35% ACx4+ Px4 protocol (Paclitaxel 175 mg /m^2). After adjuvant chemotherapy was completed, treatment was continued with trastuzumab every three weeks (first *loading* dose 8 mg/kg followed by 6 mg/kg)in different time intervals concomitant with irradiation in 77% of patients.

Cardiac function was monitored with electrocardiograpy and echocardiography by measuring left ventricle ejection fraction (LVEF) in patients before starting trastuzumab and every three months during the treatment. Cardiac dysfunction was defined as drop in LVEF by ≥ 15% of basal value or ≥ 10% of lower normal value (= 50%).

RESULTS

Follow up included 140 patients with early HER2 positive breast cancer treated with trastuzumab adjuvantly. Patients were 35 to77 years old (median 58 years). 17 patients developed symptomatic cardiac dysfunction (12.1%) of whom 6 developed severe congestive heart failure NYHA III/IV(4.2%) and 11 moderate NYHA II/III (7.9%).

Trastuzumab therapy was discontinuated in all 17 patients with symptomatic heart failureof which in 9 patients permanently (53%) and in 8 temporarily (47%) (Table 2).

First dose of trastuzumab was applied between 11 and 60 days after adjuvant chemotherapy was finished. Patients who started trastuzumab therapy 11 to 20 days after finishing chemothera-

py had 11% incidence of symptomatic heart failure, same as those patients who started trastuzumab 26 to 35 days after chemotherapy. There were no cardiac events if treatment was started 35 days after chemotherapy. Highest incidence of congestive heart failure was registered when trastuzumab was applied 21 to 25 days after adjuvant chemotherapy (22%).

Table 2.

INCIDENCE OF CONGESTIVE HEART FAILURE (CHF)

Adjuvant trastuzumab	Severe CHF (%)	Moderate CHF (%)	Asymptomatic drop in LVEF (%)	Therapy discontinuance (%)
	4.2	7.9	7.1	12.1

Table 3.

TIME OF TRASTUZUMAB APPLICATION AND CARDIAC DYSFUNCTION

Time of trastuzumab application (days)	Patients (N=140)	CHF (N=17)	CHF (%)
1-10	0	0	0
11-15	9	1	11
16-20	18	2	11
21-25	51	11	22
26-30	18	2	11
31-35	9	1	11
36-40	6	0	0
41-60	29	0	0

Statistical analysis (chi-square and post hoc tests) showed no statistically significant difference in incidence of congestive heart failure when trastuzumab was applied before 21 days or between 21 and 25 days after adjuvant chemotherapy (p= 0.374). Incidence of heart failure was significantly lower when trastuzumab was applied 25 days after adjuvant chemotherapy, comparing to earlier application (p= 0.016) (Table 3).

DISCUSSION

Our research showed 12.1% incidence of cardiac dyfunction in patients treated with trastuzumab. 4.2% of those patients had a severe cardiac failure NYHA III/IV,which is almost identical number to one shown by the NSABP-B31 and NCCTG-9831adjuvant clinical trials. It is important to notice that in those trials patients also underwent radiotherapy concomitant with trastuzumab treatment (6,16,17).

Time period between administration of chemotherapy and first application of trastuzumab has important impact on prevalence of cardiac dysfunction due to influence of postanthracycline oxidative stress and free radicals on cardiomyocytes. If trastuzumab is applied 25 days after adjuvant chemotherapy cessation, incidence of heart failure is significantly lower. Incidence is even lower when trastuzumab is applied 35 days after adjuvant chemotherapy cessation.

Similar results were shown by clinical studies. In metastatic HER2 positive breast cancer treatment studies, concomitant use of anthracycline and trastuzumab resulted in heart failure in 28% of patients, of which 16% had severe CHF. In adjuvant treatment studies, earlier application of trastuzumab (NSABP-B31, BCIRG-006 and NCCTG-9831) resulted in higher incidence of cardiac dysfunction compared to HERA study where trastuzumab was applied after cessation of adjuvant chemo and radiotherapy (16).

CONCLUSION

Time interval between cessation of adjuvant chemotherapy and first trastuzumab application has a significant impact on prevalence of trastuzumab induced cardiac dysfunction.

REFERENCES

1. Benson JR, Jato I, Keisch M, Esteva FJ, Makris A. Early breast cancer. Lancet. 2009;373(9673):1463-79.
2. Croatian National Instutute of Public Health.Croatian National Cancer Registry: Cancer incidence in Croatia 2008. Zagreb: 2010, Bulletin No 33.
3. Rayson D, Richer D, Chia S, Jackisch C at al. Antracycline-trastuzumab regimens for HER2/neu-overexpressing breast cancer: current experience and future strategies. Ann Oncol. 2008;19(9):1530-9.
4. Guglin M, Cutro R: Trastuzumab-induced cardiomyopathy. J Card Fail. 2008;14(5):437-44.
5. Cote GM, Sawyer DB, Chabner BA. ERBB2 Inhibition and Heart Failure. N Engl J Med. 2012; 367(22):2150-3.
6. Shaffer R, Tyldesley S, Rolles M at al. Acute cardiotoxicity with concurrent trastuzumab and radiotherapy including internal mammary chain nodes: a retrospective single-institutional study. Radiother Oncol. 2009; 90(1):122-6.

7. Singer CF, Köstler WJ, Hudelist G: Predicting the efficacy of trastuzumab based therapy in breast cancer: current standards and future strategies. Biochim Biophys Acta. 2008;1786(2):105-13.
8. Pentassuglia L, Sawyer DB. The role of Neuregulin-1ß/ ErbB signaling in the heart. Exp Cell Res. 2008; 315(4):627-37.
9. Xu Y, Li X, Zhou M. Neuregulin-1/ErbB signaling: a druggable target for treating heart failure. Curr Opin Pharmacol. 2009;9(2):214-9.
10. Yusuf SW, Razeghi P, Yeh ET. The diagnosis and management of cardiovascular disease in cancer patients. Curr Probl Cardiol. 2008;33(4):163-96.
11. Jones AL, Barlow M, Barrett-Lee PJ et al. Management of cardiac health in trastuzumab-treated patients with breast cancer: updated United Kingdom National Cancer Research Institute recommendations for monitoring. Br J Cancer. 2009;100(5):684-92.
12. Ewer MS, Lippman SM. Type II chemotherapy-related cardiac dysfunction: time to recognize a new entity. J Clin Oncol. 2005;23(13):2900-2 .
13. 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(31):7820-6.
14. Ewer SM, Ewer MS. Cardiotoxicity profile of trastuzumab. Drug Saf. 2008;31(6):459-67.
15. Ewer SM, Ewer MS. Anthracycline cardiotoxicity: why are we still interested? Oncology. 2009; 23(3): 234-5,239.
16. Fiuza M, Magalhães A, 2012. Trastuzumab and Cardiotoxicity, Cardiotoxicity of Oncologic Treatments. DOI: 10.5772/34093. Available from: http://www.intechopen.com/books/cardiotoxicity-of-oncologic-treatments/trastuzumab-and-cardiotoxicity . Accessed on 15.01.2014.
17. Chen T, Xu T, Li Y, Liang C, Chen J. Risk of cardiac dysfunction with trastuzumab in breast cancer patients: a meta-analysis. Cancer Treat Rev. 2011;37(4):312 -20.
18. Tarantini L,Cioffi G, Gori S,Tuccia F et al. Trastuzumab adjuvant chemotherapy and cardiotoxicity in real-world women with breast cancer. J Card Fail. 2012; 18(2):113-9.

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