

Učinci primjene trastuzumaba i trastuzumab-emtansina na QTc interval

Effects of trastuzumab and trastuzumab-emtansine on QTc intervals

 **Martina Lovrić Benčić^{1*}**,
 **Lada Bradić¹**,
 **Rea Levicki²**,
 **Juraj Jug³**,
 **Marta Begovac³**,
 **Marina Mihajlović¹**

¹ Medicinski fakultet Sveučilišta u Zagrebu, Klinički bolnički centar Zagreb, Zagreb, Hrvatska

² Opća županijska bolnica Požega, Požega, Hrvatska

³ Medicinski fakultet Sveučilišta u Zagrebu, Zagreb, Hrvatska

¹ University of Zagreb School of Medicine, University Hospital Centre Zagreb, Zagreb, Croatia

² Požega County Hospital, Požega, Croatia

³ University of Zagreb School of Medicine, Zagreb, Croatia

KLJUČNE RIJEČI: trastuzumab, trastuzumab s emtansinom, QTc interval, HER2+ karcinom dojke.

KEYWORDS: trastuzumab, trastuzumab-emtansine, QTc interval, HER2+ breast cancer.

CITATION: *Cardiol Croat.* 2018;13(11-12):466-467. | <https://doi.org/10.15836/ccar2018.466>

***ADDRESS FOR CORRESPONDENCE:** Martina Lovrić Benčić, Klinički bolnički centar Zagreb, Kišpatičeva 12, HR-10000 Zagreb, Croatia. / Phone: +385-91-228-2240 / Email: mlbencic@icloud.com

ORCID: Martina Lovrić Benčić, <https://orcid.org/0000-0001-8446-6120> • Lada Bradić, <https://orcid.org/0000-0001-8296-699X> Rea Levicki, <https://orcid.org/0000-0003-3687-1310> • Juraj Jug, <https://orcid.org/0000-0002-3189-1518> Marta Begovac, <https://orcid.org/0000-0003-0263-339x> • Marina Mihajlović, <https://orcid.org/0000-0002-0027-9676>

Uvod: Trastuzumab i trastuzumab-emtansin su lijekovi, tj. antitijela, odnosno konjugat antitijela i emtansina za humani epidermalni faktor rasta receptora 2 (HER2) - pozitivni karcinom dojke. Njihove moguće nuspojave mogu biti produljenje QT i smanjenje ejskcijske frakcije lijevog ventrikula (LVEF), kao što je prethodno opisano u literaturi.¹⁻³

Metode i rezultati: Sve prikazane bolesnice su prethodno liječene početnom standardnom kombinacijom paklitaksel i karboplatine. Nakon toga dobile su trastuzumab, pa trastuzumab-emtansin. Cilj ove studije bio je ispitati njihov učinak na QTc interva. Ukupno 26 bolesnica s očuvanom LVEF liječeno je trastuzumabom i prije svake primjene lijeka sniman je i analiziran EKG. 24 bolesnice (prosječne dobi 57,33 godine; 46-69 godina) su nastavile liječenje trastuzumab-emtansinom zbog metastatske bolesti. Dvije su bolesnice zbog pada LVEF-a obustavile liječenje. Posljednji EKG je snimljen 6 mjeseci nakon posljednje doze lijeka. Značajno produljenje QTc intervala primijećeno je nakon treće primjene oba lijeka, nastavljeno je tijekom četvrte, pete i šeste primjene oba lijeka, a normalizacija QTc intervala primijećena je nakon šest mjeseci bez terapije. Rezultati su prikazani u **tablicama 1, 2 i 3**.

Zaključak: Liječenje trastuzumabom i trastuzumab-emtansinom značajno produžuje QTc interval u bolesnica s HER2 pozitivnim karcinomom dojke, ali je taj učinak bio reverzibilan.

Introduction: Trastuzumab and trastuzumab-emtansine are antibody drugs and antibody-conjugate for human epidermal growth factor receptor 2 (HER2)- positive breast cancer. Their possible side effects can be QT prolongation and reduction of left ventricular ejection fraction (LVEF), as previously documented.¹⁻³

Methods and Results: All patients were previously treated with standard regimen: paclitaxel and cisplatin. After that they received specific antibody drugs. The aim of this study was to test their effect on QTc interval in our patients. A total of 26 patients with preserved LVEF were treated with trastuzumab and before every application, ECG was obtained and analyzed. Later on, 24 patients (aged 57.33 years; 46-69 years) continued the treatment with trastuzumab-emtansine because of metastatic disease. Due to reduction of LVEF two patients could not continue with therapy. The last ECG was obtained 6 months after the last drug application. Statistical analysis was performed using standard t-test. Significant QTc prolongation was noticed after the third application of both drugs, continued during the fourth, fifth and sixth application of both drugs and normalization was noticed after six months without therapy. Results are shown in **tables 1, 2 and 3**.

Conclusion: Treatment with trastuzumab and also with trastuzumab-emtansine significantly prolonged QTc interval in patients with breast cancer, but the change was reversible after the cessation of treatment.

TABLE 1. Average duration of QTc intervals.

	Average duration of QTc intervals (ms)	
	TRASTUZUMAB	TRASTUZUMAB+EMTANSIN
Before th.1	447.4750	448.6250
4	469.8750	470.1250
5	471.0833	474.4583
6	469.6667	471.8750
6 months after administration of the last dose 7	451.4583	454.4167

RECEIVED:
October 26, 2018

ACCEPTED:
November 5, 2018



TABLE 2. Statistical significance of QTc prolongation compared to initial values (QTc1).

QTc interval - comparison	p-value TRASTUZUMAB	CI (95%) TRASTUZUMAB	p-value TRASTUZUMAB+EMTANSINE	CI (95%) TRASTUZUMAB+EMTANSINE
QTc1 vs QTc4	0.007907	6.192 – 38.807	0.002223	8.143 – 34.857
QTc1 vs QTc5	0.002470	8.809 – 38.607	0.000605	11.714 – 39.953
QTc1 vs QTc6	0.005007	7.072 – 37.511	0.000757	10.280 – 36.219

TABLE 3. Statistical significance of QTc prolongation compared to the control value 6 months after the last drug application (QTc7).

QTc interval - comparison	p-value TRASTUZUMAB	CI (95%) TRASTUZUMAB	p-value TRASTUZUMAB+EMTANSINE	CI (95%) TRASTUZUMAB+EMTANSINE
QTc7 vs QTc4	0.022461	2.722 – 34.111	0.018883	2.717 – 28.699
QTc7 vs QTc5	0.007911	5.399 – 33.851	0.005280	6.267 – 33.816
QTc7 vs QTc6	0.015374	3.648 – 32.768	0.007633	4.865 – 30.051

LITERATURE

- Gupta M, Wang B, Carrothers TJ, LoRusso PM, Chu YW, Shih T, et al. Effects of Trastuzumab Emtansine (T-DM1) on QT Interval and Safety of Pertuzumab Plus T-DM1 in Patients With Previously Treated Human Epidermal Growth Factor Receptor 2-Positive Metastatic Breast Cancer. *Clin Pharmacol Drug Dev.* 2013 Jan;2(1):11-24. <https://doi.org/10.1002/cpdd.9>
- Perez EA, Romond EH, Suman VJ, Jeong JH, Davidson NE, Geyer CE Jr, et al. Four-year follow-up of trastuzumab plus adjuvant chemotherapy for operable human epidermal growth factor receptor 2-positive breast cancer: joint analysis of data from NCCTG N9831 and NSABP B-31. *J Clin Oncol.* 2011 Sep 1;29(25):3366-73. <https://doi.org/10.1200/JCO.2011.35.0868>
- Tanriverdi O, Meydan N, Barutca S. Long-term effect of trastuzumab on QT dispersion in adjuvant treatment for patients with Her2 receptor positive breast cancer: a pilot study. *Med Oncol.* 2012 Dec;29(5):3265-71. <https://doi.org/10.1007/s12032-012-0291-z>