Kardiotoksičnost uzrokovana trastuzumabom – šestogodišnje iskustvo

Trastuzumab cardiotoxicity – six-year experience

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Uvod: Kardiotoksičnost je najvažnija nuspojava trastuzumaba, humaniziranog monoklonskog protutijela na HER2 protein, koji se koristi u imunoterapiji raka dojke. Najčešće se javlja kao reverzibilna disfunkcija miokarda te često nakon privremenog prekida terapije dolazi do oporavka srčane funkcije i moguć je nastavak onkološkog liječenja.[1-3]

Pacijenti i metode: Od početka 2009. do kraja 2015. prospektivno je praćeno 496 bolesnica s nemetastaskim karcinomom dojke liječenih adjuvantno trastuzumabom u Kliničkom bolničkom centru Sestre milosrdnice (420 u Klinici za tumore i 76 u Klinici za onkologiju i nuklearnu medicinu). Kardiotoksičnost je definirana smanjenjem istisne frakcije lijeve klijetke (LVEF) za 15% od početne ili za 10% ispod donje granice normale. Transtorakalna ehokardiografija je učinjena svim bolesnicama prije početka terapije te u tromjesečnim kontrolama za vrijeme trajanja liječenja. Ukoliko je utvrđena kardiotoksičnost prekinuta je terapija trastuzumabom s mjesečnim ehokardiografskim kontrolama.

Rezultati: Kardiotoksičnost je utvrđena u 54 bolesnice (10,88%), kod većine (88%) u prvih 6 mjeseci od početka terapije. Nakon prekida trastuzumaba potpuni oporavak zabilježen u njih 28 (51,85%) te je u njih završeno onkološko liječenje. Zbog nepotpunog oporavka srčane funkcije liječenje trastuzumabom nije završilo 26 bolesnica (48,14%). Prosječna LVEF pri postavljanju dijagnoze kardiotoksičnosti iznosila je 44,18% (20-52%). U bolesnica s ireverzibilnim smanjenjem sistoličke funkcije zabilježena je značajno veći pad LVEF nego u onih s reverzibilnim (27:15 %, p<0,0001), te bolesnice su imale i značajno više razine serumskog NT-proBNP-a (134,7:92,3 ng/L, p=0,01) a u njih je terapija trastuzumabom započeta ranije nakon prethodne kemoterapije (27:33,5 dana, p=0,037). Samo je 6 bolesnica imalo simptome umjerenog do teškog zatajivanja srca.

Zaključak: Kardiotoksičnost uzrokovana trastuzumabom javlja se u oko 10% bolesnica uglavnom u prvih 6 mjeseci od početka terapije. Vjerojatnije će biti ireverzibilna u bolesnica s izraženijim padom LVEF i višim serumskim razinama NT-proBNP-a. Također je veća vjerojatnost pojave ireverzibilne srčane disfunkcije ukoliko je vrijeme između prethodne kemoterapije i trastuzumaba bilo kraće od 30 dana.

Purpose: Cardiotoxicity is the most important side effect of trastuzumab, humanized monoclonal antibody to the HER2 protein, in use for immunotherapy of breast cancer. It is mainly manifested as a reduction in left ventricular contractility and the process is therefore mostly reversible. Temporary cessation of therapy often leads to recovery of cardiac function, and it is possible to continue the oncology treatment.[1-3]

Patients and Methods: Since the beginning of 2009 until the end of 2015, we have analyzed 496 patients (pts) with non-metastatic breast cancer, treated with trastuzumab for one year with the standard adjuvant therapy protocol. Cardiotoxicity was defined with the reduction of left ventricular ejection fraction (LVEF) by 15% from the baseline or by 10% of normal values. Echocardiography was performed before the beginning and in three months period during therapy. If cardiotoxicity was established, pts were suspended from the trastuzumab therapy, with monthly echocardiography controls.

Results: Cardiotoxicity was established in 54 pts (10.88%), most commonly in the first 6 months of starting treatment. Complete recovery of the cardiac function was found in 28 pts (51.85%) and they managed to finish trastuzumab protocol. Due to only partial recovery of the cardiac function or cardiotoxicity after readministration, trastuzumab therapy was not finished in 26 pts (48.14%). At the time when diagnosis of the cardiotoxicity were established average LVEF was 44.18% (20-52%). Pts with irreversible cardiotoxicity had significantly greater reduction of LVEF (15:27 %, p<0.0001), higher mean serum level of NT-proBNP (134.7:92.3 ng/L, p=0.01) and in those pts trastuzumab was started earlier after prior chemotherapy (27:33.5 days, p=0.037). Only 6 pts had symptomatic moderate or severe heart failure.

Conclusion: Trastuzumab cardiotoxicity occurs in about 10% of patients mainly in the first 6 months of therapy. It is more likely to be irreversible in pts with a more extensive decrease of the LVEF and a higher serum NT-proBNP level. The time between prior chemotherapy and administration of trastuzumab shorter than 30 days is more often associated with irreversible cardiac impairment.

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