Intern Emerg Med (2012) 7:399–401
DOI 10.1007/s11739-012-0845-2

IM - COMMENTARY

# Renal dysfunction and increased risk of cardiotoxicity with trastuzumab therapy: a new challenge in cardio-oncology

**Adriana Albini · Francesco Donatelli · Chiara Focaccetti · Mario Milco D'Elios · Douglas M. Noonan**

Received: 15 June 2012 / Accepted: 8 August 2012 / Published online: 2 September 2012


In the current era of cardio-oncology the awareness of the cardiotoxicity of anti-cancer therapies is entering into common clinical practice, and new methods for monitoring risk and early markers are urgently needed [1–3]. One of the clear examples of cancer therapy cardiotoxicity is in patients with breast cancer over-expressing the HER2 receptor, which are currently treated with anthracyclines or taxanes and with trastuzumab. Anthracyclines and trastuzumab are both associated with cardiotoxicity [1]. Trastuzumab is associated with cardiotoxicity through a variety of HER2-related and unrelated mechanisms [4]. Concurrent use of anthracyclines and trastuzumab, while highly effective, are found to synergize in inducing cardiac damage [2]. In this issue of Internal and Emergency Medicine, Russo et al. [5] point out a new risk condition in cancer chemotherapy-associated cardiotoxicity: impaired renal function. In particular, there is renal dysfunction (RD) in a group of women with breast cancer (the ICARO cohort) with no previous signs or symptoms of heart failure and preserved LVEF who are undergoing trastuzumab treatment after chemotherapy. The authors examine this dysfunction and its relation to cardiac toxicity following trastuzumab.

The heart–kidney axis is well known in cardiology, where RD often aggravates congestive heart failure. RD has now been identified as a risk factor for mortality [6], in particular increased risk for cardiovascular (CV) events. Diverse mechanisms are associated with these effects, including perturbation of the renin–angiotensin system, atrial natriuretic peptide signalling and the sympathetic baroreflex system, most of which are related to hypertension. The importance of sympathetic baroreflex signaling by the kidneys in inducing cardiac stress is increasingly recognized, to the point that trials on ablation of renal sympathetic signaling in hypertensive patients are underway [7]. However, the role of RD as a risk factor for CV events in cancer therapy has to date not been entered into the cardio-oncologic equation.

Anthracyclines, taxanes or trastuzumab alone, at present are not considered to be nephrotoxic, and current guidelines do not require dose reduction in patients with RD. Russo et al. [5] report that RD, determined by estimation of GFR using creatine clearance (eGFR) with the simplified MDRD equation, assessed at baseline (prior to trastuzumab therapy, after other chemotherapies) is associated with an increased risk of cardiovascular toxicity and complications following trastuzumab. Cardiotoxicity was monitored by

A. Albini (✉)
Research Infrastructure, IRCCS Arcispedale Santa Maria Nuova, Reggio Emilia, Italy
e-mail: albini.adriana@gmail.com

A. Albini
Polo Scientifico e Tecnologico, MultiMedica Onlus, Milan, Italy

F. Donatelli
Department of Clinical and Community Sciences, University of Milan, Milan, Italy

F. Donatelli
Department of Cardiovascular and Metabolic Disease, IRCCS MultiMedica, Milan, Italy

C. Focaccetti · D. M. Noonan
Polo Scientifico e Tecnologico, IRCCS MultiMedica, Milan, Italy

M. M. D'Elios
Patologia Medica, AOU Careggi Hospital, University of Florence, Florence, Italy

D. M. Noonan
Department of Biotechnologies and Life Sciences, University of Insubria, Varese, Italy

assessment of left ventricular ejection fraction (LVEF) at baseline and after 3, 6, 9 and 12 months and for clinical signs of congestive heart failure (CHF), RD was based on the K/DOQI classification from class I to V.

Russo et al. observe that the prevalence of trastuzumab-induced cardiotoxicity parallels the severity of RD ranging from 15 % (in patients in class I RD) to 38 % (in patients in class III RD). The best prognostic cut-off value for cardiotoxicity of eGFR is 78 ml/min/1.73 $m^2$, also implying that a mild impairment of renal function is sufficient to expose these patients to cardiac damage. The patients who experienced trastuzumab-associated cardiotoxicity, as compared to those who had no cardiotoxicity, are also older, and tend to be those treated with doxorubicin. However, the prevalence of hypertension, diabetes, and dyslipidemia is similar between the two groups, suggesting that RD associated hypertension is not the primary mechanism.

When Russo et al. determined renal function prior to trastuzumab therapy, most of the patients studied had prior anthracycline or other chemotherapy (anthracyclines 88 %, cyclophosphamide 89 %, taxanes 44 %, 5-fluorouracil 46 %, neoadjuvant 25 %) [5]. The majority of the patients had stage one RD, only 30 % of the subjects showed normal renal function. It is not clear if RD was already present prior to chemotherapy in this population (30 % were above 60), or if this was already induced or worsened by anthracycline or other chemotherapy. Renal function clearly declines with age, and several studies have shown a decrease in average GFR with age [8–11], and may represent a potential bias of the study. The InCHIANTI data [12] provide a potential control population (Table 1), although the GFR rates were measured using a different formula and the average age of the Russo et al. [5] cohort is younger (55.1 ± 10.9 vs. 76.0 ± 6). If we compare the GFR rates of that found by Russo et al. following anthracyclin therapy to that of the women in the InCHIANTI population, somewhat similar results are found: the majority of the patients are in class II with mild RD (Table 1). The more elderly InCHIANTI population shows fewer individuals with normal renal function and more with class III RD, as do the Russo et al. population examining those individuals over 60.

These data imply that it is probably not chemotherapy that is creating RD in the ICARO cohort, it appears that frequent RD is a baseline characteristic of the cohort. Although those experiencing cardiotoxicity are significantly older, the differences are more pronounced with low eGFR, indicating that it is not age alone, but RD per se, that is associated with cardiotoxicity after trastuzumab. In the ICARO cohort, RD is also noted in younger individuals, raising the possibility of some degree of chemotherapy (or possibly cancer) induced RD. As mentioned above, while current data do not associate anthracyclines, taxanes or trastuzumab with nephrotoxicity, as pharmacovigilance expands into the cardio-oncology arena [13], the data of Russo et al. [5] suggest that careful evaluation of renal function needs to be included as part of the "onco-pharmacovigilance" approach [3, 13].

**Table 1** Comparison of rates of RD in the InCHIANTI (untreated) cohort with that of Russo et al. (most treated with chemotherapy)

| Kidney Function (eGFR) | Russo et al. [5] (all women) | Russo et al. [5] (women >60) | InCHIANTI [2] (women) |
|---|---|---|---|
| Class I (normal) >90 | 30 % | 15 % | 18.3 % |
| class II (mild RD) | 61 % (eGFR 60–89) | 69 % (eGFR 60–89) | 40.6 % (eGFR 61–90) |
| class III (moderate RD) | 9 % (eGFR 30–59) | 16 % (eGFR 30–59) | 37.8 % (eGFR 31–60) |
| (severe RD) <30 | 0 % | 0 % | 3.3 % |

The report by Russo et al. indicate that renal function is an additional risk factor to take into account in the cardio-oncological evaluation prior to therapy, helping to predict those patients at risk. Whether RD is directly or indirectly involved in exacerbating the cardiotoxicity of cancer therapies, or if it is simply a condition to be taken into account when determining risk, remains to be answered by further studies. Since serum creatinine-based formulas have been reported to overestimate impairment of kidney function in the elderly InCHIANTI population [10], an assessment of renal function using creatinine clearance based on 24 h urine collection should also be examined in future studies.

Understanding the effects of chemotherapy on renal function will be the next step in determining the utility of monitoring renal function in cardio-oncology as well as shedding light on the potential mechanisms involved. This is particularly important in light of possible prevention approaches [1], where RD may be an indicator of those patients more likely to have trastuzumab-related cardiotoxicity. For example, ACE inhibitors are widely employed for protection of both cardiovascular and renal function, identification of high-risk patients may warrant preventive use of these compounds.

Russo et al. study opens many new and important avenues for investigation: (1) What are the effects of chemotherapy on renal function? (2) The mechanisms linked to the enhancement of trastuzumab cardiotoxicity; is it increased risk or alterations in the metabolic/therapeutic/cardiac response to trastuzumab that plays the leading role?

(3) Is this valid only for trastuzumab alone or can this be extended to other chemotherapy and targeted agents that are associated with cardiotoxicity?

These questions need to be answered by further studies, and the cardioncology research network needs to keep these points in mind when developing future investigations to answer the puzzles associated with cardiotoxicity, and to find ways of predicting and avoiding these potentially severe complications.

**Acknowledgments** The authors were supported by funds of the University of Insubria, MultiMedica Onlus, the AIRC (Associazione Italiana per la Ricerca sul Cancro), the MIUR GPS DM28938, and the University of Florence.

**Conflict of interest** None

## References

1. Albini A, Pennesi G, Donatelli F, Cammarota R, De Flora S, Noonan DM (2010) Cardiotoxicity of anticancer drugs: the need for cardio-oncology and cardio-oncological prevention. J Nat Cancer Inst 102:14–25
2. Ewer MS, Ewer SM (2010) Cardiotoxicity of anticancer treatments: what the cardiologist needs to know. Nat Rev Cardiol 7:564–575
3. Albini A, Donatelli F, Noonan D, D'Elios MM, Prisco D (2012) Bringing new players into the field: onco-pharmacovigilance in the era of cardio-oncology. Intern Emerg Med 7:99–101
4. Albini A, Cesana E, Donatelli F, Cammarota R, Bucci EO, Baravelli M et al (2011) Cardio-oncology in targeting the HER receptor family: the puzzle of different cardiotoxicities of HER2 inhibitors. Future Cardiol 7:693–704
5. Russo G, Cioffi G, Di Lenarda A, Tuccia F, Bovelli D, Di Tano G et al (2012) Role of renal function on development of cardiotoxicity associated with trastuzumab-based adjuvant chemotherapy for early breast cancer. Intern Emerg Med. doi:10.1007/s11739-012-0794-9
6. Matsushita K, van der Velde M, Astor BC, Woodward M, Levey AS, de Jong PE et al (2010) Association of estimated glomerular filtration rate and albuminuria with all-cause and cardiovascular mortality in general population cohorts: a collaborative meta-analysis. Lancet 375:2073–2081
7. Hering D, Mahfoud F, Walton AS, Krum H, Lambert GW, Lambert EA et al (2012) Renal denervation in moderate to severe CKD. J Am Soc Nephrol 23(7):1250–1257
8. Eriksen BO, Ingebretsen OC (2006) The progression of chronic kidney disease: a 10-year population-based study of the effects of gender and age. Kidney Int 69:375–382
9. O'Hare AM, Choi AI, Bertenthal D, Bacchetti P, Garg AX, Kaufman JS et al (2007) Age affects outcomes in chronic kidney disease. J Am Soc Nephrol 18:2758–2765
10. Giannelli SV, Patel KV, Windham BG, Pizzarelli F, Ferrucci L, Guralnik JM (2007) Magnitude of underascertainment of impaired kidney function in older adults with normal serum creatinine. J Am Geriatr Soc 55:816–823
11. Giannelli SV, Graf CE, Herrmann FR, Michel JP, Patel KV, Pizzarelli F et al (2011) Natural history of older adults with impaired kidney function: the InCHIANTI study. Rejuvenation Res 14:513–523
12. Ble A, Fink JC, Woodman RC, Klausner MA, Windham BG, Guralnik JM et al (2005) Renal function, erythropoietin, and anemia of older persons: the InCHIANTI study. Arch Intern Med 165:2222–2227
13. Raschi E, De Ponti F (2012) Cardiovascular toxicity of anticancer-targeted therapy: emerging issues in the era of cardio-oncology. Intern Emerg Med 7:113–131