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Trastuzumab-related cardiotoxicity: what do we know in 2020?

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Trastuzumab, a humanized monoclonal antibody against the human epidermal growth factor receptor 2 (HER2), has transformed treatment outcomes for patients with HER2-positive breast cancer (1). Trastuzumab-related cardiotoxicity (TRC) remains the most common cause of treatment interruption. The spectrum of TRC ranges from mild, asymptomatic reduction in left ventricular ejection fraction (LVEF) to fulminant congestive cardiac failure (CCF) and cardiac death. Mechanisms of TRC are now well understood to be distinct from that of anthracycline-induced TRC and largely due to reversible suppression of cardiomyocyte HER2 signaling (2). However, the identification of predictive biomarkers of TRC, and the benefit of pharmacological agents to prevent TRC has been controversial to date and an area of ongoing research interest.

A 2012 Cochrane meta-analysis (3) identified eight studies of trastuzumab in HER2-positive early breast cancer. This included the four landmark RCTs (NCCTG N9831, NSABP B-31, HERA trial, BCIRG-006) (4-6). The meta-analysis found that the addition of adjuvant trastuzumab to chemotherapy improved disease-free survival (HR: 0.66, 95% CI: 0.57-0.77, $P < 0.00001$) and overall survival (HR: 0.6, 95% CI: 0.5-0.71, $P < 0.00001$) (3). The benefits of trastuzumab were observed irrespective of tumor stage, hormone receptor status or age. Consequently, 1 year of adjuvant trastuzumab has now been accepted as the standard of care.

However, the rates of reported cardiac toxicity associated with trastuzumab differed across individual trials. For example, reported rates of asymptomatic LVEF decline ranged from 7% in the HERA trial (5) to 18.9% in the

BCIRG-006 trial (6). Furthermore, rates of Grade III/IV CCF/cardiac death events ranged from 0% in the FinHer Study [utilizing 9 weeks of adjuvant trastuzumab given with docetaxel alone (7)] to 4.1% in the NSABP B-31 trial (8). In the Cochrane meta-analysis, 135 (2.5%) patients developed CCF on the trastuzumab arms compared to 20 (0.4%) patients amongst control arms (RR: 5.11, 90% CI: 3-8.72, $P < 0.00001$). Meanwhile, LVEF decline occurred in 11.2% of cases *vs.* 5.6% of controls (RR: 1.83, 90% CI: 1.36-2.47, $P = 0.0008$) (3). Reasons for differing rates of TRC across studies include differences in study design, schedule of LVEF monitoring, partner chemotherapy drugs administered, patient population recruited, and definitions of TRC.

The recently reported individual patient data meta-analysis by de Azambuja and colleagues of the NSABP B-31, NCCTG N9831 and HERA trials provides some more granular information on the timing of TRC and risk factors associated with its occurrence (9). Dr. de Azambuja and colleagues should be congratulated for generating a detailed dataset on TRC from randomized trials using individual patient data, and their meta-analysis provides an up-to-date reference for clinicians and researchers interested in this problem. The meta-analysis included 7,445 patients, with 4,017 patients treated in the trastuzumab arm and 3,439 patients in the control arm. All patients on the NSABP B-31 and NCCTG N9831 received doxorubicin and cyclophosphamide followed by paclitaxel chemotherapy, whereas on the HERA trial at least an anthracycline $\pm$ taxane was administered in the vast majority (94%) of patients. All patients in the meta-analysis who received

anthracyclines did so prior to trastuzumab, whereas paclitaxel was given concurrently with trastuzumab in 59.5% and sequentially in the remainder. The meta-analysis would have been strengthened with the inclusion of patients on the BCIRG-006 trial, as it contained a large population of patients who did not receive anthracyclines (6), given the use of anthracyclines in early-stage HER2+ breast cancer remains an ongoing issue of debate (10).

Consistent with the previously reported Cochrane meta-analysis, prevalence of TRC in patients treated with trastuzumab was 11.3%, with the majority of these events being an asymptomatic or mildly symptomatic LVEF decline (8.7%) (9). The prevalence of TRC events in the combined control arm was not reported. Rates of symptomatic CCF and cardiac deaths were low with seven deaths in the trastuzumab arm and five in the control arm. Severe CCF (NYHA Grade III–IV) occurred in 2.3% in the trastuzumab arm *vs.* 0.8% in the control arm. Of interest, only 48/452 patients (10%) who developed TRC had this occur >28 days after the completion of trastuzumab (9). Although there was an excess of 10 years of median follow-up for efficacy outcomes, long-term toxicity outcomes, including trajectory of cardiac recovery, was not able to be reported due to heterogeneous data available on late LVEF monitoring across the studies. In the NSABP B-31 study, 31 patients (4.1%) in trastuzumab group developed CCF, of which only 1/27 who were followed after 6 months after the onset of CCF had persistent symptoms (11).

Several baseline characteristics are known to be associated with increased risk of TRC from the individual trials, and the findings from the recent individual patient data meta-analysis are not surprising. Low baseline LVEF <60%, high BMI (>25), history of hypertension and age (≥ 60) were associated with increased TRC risk, with the presence of multiple (>2) risk factors doubling the relative risk of TRC (9). It is important to highlight here that the definition of ‘baseline’ LVEF differs across studies, with the HERA study recruiting patients at the end of all (neo)adjuvant chemotherapy, and thus only the post-anthracycline LVEF would be available in this cohort as the study baseline. Pre-anthracycline LVEF or true ‘baseline’ LVEF data was available from the NCCTG N9831 and NSABP B-31 studies, and decreased LVEF post-anthracycline of $\geq 16\%$ was an exclusion criterion (4). Prospective data from the Cardiotoxicity of Adjuvant Trastuzumab Study (CATS) showed that decline in LVEF from pre- to post-anthracycline were associated with TRC in a multicenter Australian cohort (odds ratio: 7.9,

$P < 0.0001$) (12). Clinicians should therefore consider both pre-anthracycline and post-anthracycline LVEF values, together with patients’ comorbidities and age to determine their absolute risk of cardiotoxicity with trastuzumab.

Where multiple risk factors exist, or a history of CCF is present, data from the BCIRG-006 study found that the anthracycline-free regimen of carboplatin, docetaxel and trastuzumab (TCH) for 1 year was associated with a lower risk of asymptomatic LVEF decline (9.4%) and CCF (0.4%) compared to doxorubicin, cyclophosphamide, docetaxel and trastuzumab (18.6% LVEF decline, 2% CCF) (6). An exploratory finding from the meta-analysis is that sequential trastuzumab following paclitaxel chemotherapy was associated with a numerically lower rate of TRC (6.9%) compared to concurrent trastuzumab and paclitaxel chemotherapy (17.7%) (9). The difference was largely due to a higher proportion of patients with asymptomatic/mildly symptomatic LVEF decline (13.8% *vs.* 5.3%). The reason for this difference may be explained by two factors. Firstly it may be simply an artefact due to study design, given that randomization occurred after AC treatment in the studies of sequential trastuzumab administration, thus patients with AC-related cardiotoxicity would have been excluded, whereas in the studies that randomized prior to AC treatment, patients who developed AC-related cardiotoxicity may have been excluded from trastuzumab, but were still included in the intent-to-treat analyses. Secondly, sequential administration of trastuzumab after taxanes results in a longer delay between anthracycline treatment and initiation of trastuzumab, allowing more time for cardiac recovery. However, given that concurrent trastuzumab was associated with a trend towards better disease-free survival in the N9831 trial compared to sequential treatment (13), it is difficult to make a compelling case to administer trastuzumab sequentially to adjuvant chemotherapy, and TCH should be favored in patients with high risk of TRC.

A limitation when applying the results of the meta-analysis by de Azambuja and colleagues to contemporary clinical practice is only a very small proportion of patients received neoadjuvant treatment, and none received contemporary anti-HER2 therapies such as pertuzumab, T-DM1, and neratinib. Given the benefit of neoadjuvant pertuzumab (14) and adjuvant TDM1 (15), many patients with locally advanced HER2+ breast cancer are now treated with neoadjuvant chemotherapy. More data is required on cardiotoxicity rates when trastuzumab is used in the neoadjuvant setting. In a meta-analysis of five trials including

515 patients randomized to trastuzumab plus neoadjuvant chemotherapy versus neoadjuvant chemotherapy alone, pathological complete response rates were increased with the addition of trastuzumab. Cardiotoxicity rates were low in these trials, although all required a baseline LVEF >55% compared to the adjuvant trials which generally allowed patients with baseline LVEF >50% (16). Reassuringly, the addition of pertuzumab to trastuzumab for the treatment of metastatic HER2+ breast cancer was not associated with higher rates of cardiotoxicity or asymptomatic LVEF decline (17). While TDM1 and neratinib have also not been shown to be associated with high rates of cardiotoxicity to date (18), this is an area requiring further study in the real-world context given the highly selected nature of patients enrolled into clinical trials.

Identification of biomarkers to predict for and allow earlier identification and treatment of TRC remains an area of active interest in the cardio-oncology field. Although elevated serum biomarkers have been associated with anthracycline-related toxicity, the predictive and prognostic benefit of routine troponin T, troponin I and BNP monitoring is controversial (12,19). Given the measurement variability particularly with LVEF monitoring by transthoracic echocardiogram, myocardial deformation imaging using cardiac global longitudinal strain (GLS) is increasingly used in research settings (20). GLS has shown to precede LVEF decline, potentially allowing a window for intervention using pharmacological agents such as beta blockers or ACE-I to prevent further LVEF decline (21). Further studies are warranted to identify whether biomarkers of TRC and pharmacoprotective agents can reduce treatment interruptions for patients on trastuzumab. One example of this is the Strain Surveillance during Chemotherapy for Improving Cardiovascular Outcomes (SUCCOUR) study which is a multicenter randomized study examining whether GLS monitoring of cardiac function compared to traditional LVEF monitoring, coupled with early adoption of pharmacoprotective agents results in improved outcomes for patients on chemotherapy and trastuzumab (22).

In summary, the meta-analysis of NSABP B31, NSABP B-31, NCCTG N9831 and HERA trials confirms in large part what is known about risk factors and the clinical course for TRC, a gratifying result from this study of individual patient data. However, there has yet to be a consensus on the optimal biomarkers to identify TRC early, and whether cardioprotective agents have a role in reducing TRC, given the low rates of symptomatic heart failure and fatal cardiac

events from trastuzumab. The arsenal of anti-HER2 drugs being used in the clinic is increasingly complex, and this is coupled by rising medical comorbidities in cancer patients. Therefore, ongoing collaboration between cardiologists and oncologists is required to advance the field both in a clinical and research setting.

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