Report from the Canadian Association of Medical Oncology Annual Meeting

Cardiotoxicity in breast cancer

BALANCING CARDIOTOXICITY AND SURVIVAL BENEFITS

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TRIAL SUMMARY: Cardiac risk and trastuzumab

Rushton M, Lima I, Johnson C, et al. Balancing the risks versus benefits of trastuzumab: a call to action for oncologists, cardiologists and cardio-oncologists. Canadian Association of Medical Oncology Annual Meeting. April 26, 2018, Toronto. Abstract 10.

This Ontario study evaluated the impact of routine cardiac imaging on disease-free (DFS) and overall survival (OS) in early-stage HER2-positive breast cancer. A retrospective population-based cohort study looked at early-stage breast cancer patients treated with adjuvant trastuzumab in Ontario between 2007 and 2016. Patient-level data was sourced through the Institute for Clinical Evaluative Sciences, which captures all patients in Ontario.

The cohort was divided into 3 arms: patients in arm A had received 17 or 18 cycles of trastuzumab and experienced no cardiotoxicity; patients in arm B experienced no cardiotoxicity, but had stopped trastuzumab after ≤16 cycles within 30 days of last cardiac imaging; patients in arm C had developed cardiotoxicity. Cardiotoxicity was defined as a new diagnosis of heart failure (HF), cardiomyopathy (CM) or pulmonary edema within 90 days of the last cycle of trastuzumab. The primary outcome was DFS; secondary outcomes were OS, cancer-specific OS, and cardiovascular mortality. Survival analysis was performed using Cox and sub-distribution hazard models.

Results: A total of 4,820 patients met the inclusion criteria; 4,018 in arm A, 442 in arm B, and 360 in arm C. The median number of cycles of trastuzumab received was 18 in arm A, 13 in arm B, and 14 in arm C. Five-year DFS was significantly worse in arms B (70.3%; 95% CI: 63.5–74.7) and C (74.9%; 69.5–79.5) than in arm A (93.2%; 92.3–94.0). Hazard ratios for DFS were 2.96 (2.35–3.72) for arms B and C combined, and 2.41 (1.87–3.12) for arm A. As well, 5-year OS was significantly worse in arms B (75.4%) and C (80.1%) than in arm A (95.2%); HR for OS was 3.99 (3.10–5.14) for arms B and C combined and 2.98 (2.24–3.95) for arm A. All p-values were <0.05.

Breast cancer patients in Ontario who did not complete 17 cycles of adjuvant trastuzumab had significantly worse DFS and OS than patients who received at least 17 cycles. A significant population stopped trastuzumab shortly after cardiac imaging, without developing cardiotoxicity, likely due to detection of asymptomatic drops in left ventricular ejection fraction (LVEF). These findings support the need to consider strategies that enable patients to continue cancer therapy following abnormal cardiac imaging. These may include concurrent optimization of cardiac function and cardiac risk factors.

TRIAL SUMMARY: Cardiac assessment prior to chemotherapy

O'Brien P, Matheson K, Jeyakumar A, et al. The clinical utility of baseline cardiac assessments prior to adjuvant anthracycline chemotherapy in breast cancer: a systematic review and meta-analysis. Canadian Association of Medical Oncology Annual Meeting. April 26, 2018, Toronto. Abstract 36.

In clinical practice, cardiac assessment with multigated acquisition (MUGA) scan or echocardiography (ECHO) is commonly performed prior to anthracycline-based adjuvant chemotherapy. However, outside of clinical trials, the utility of these routine baseline cardiac assessments in patients with early-stage breast cancer is uncertain. The objectives of this study were to determine the clinical impact of routine baseline cardiac assessments prior to anthracycline-based adjuvant chemotherapy for early-stage breast cancer, and to identify patients in whom baseline cardiac assessments may not be warranted.

A search was performed to identify all observational

studies, meeting predefined criteria, of MUGA and/or ECHO undertaken before commencing anthracycline-based adjuvant chemotherapy in early breast cancer. The outcomes of interest in this systematic review and meta-analysis included rates of abnormal baseline LVEF and changes in chemotherapy decisions following cardiac assessments.

Results: Of 1,401 citations retrieved, 8 studies met our predefined criteria. Six studies (number of patients=2,545) reported rates of abnormal LVEF, and 6 (number of patients=1,713) investigated the impact of baseline LVEF assessment on chemotherapy decisions. Overall, 2.5% of patients (95% CI: 2.0%–4.0%) had abnormal baseline LVEF and 1.6% (95% CI: 1.0%–3.0%) had a change in chemotherapy decision related to the assessment. These outcomes varied according to LVEF assessment modality (ECHO vs MUGA vs both), publication type (abstract vs manuscript), and inclusion of metastatic disease (yes vs no). The authors found no consistently identified risk factors that correlated with abnormal baseline LVEF.

Routine baseline cardiac assessments prior to anthracycline-based adjuvant chemotherapy in early breast cancer patients reveal low rates of abnormal LVEF and only infrequently affect clinical management. Future studies should examine correlations with underlying cardiac risk factors in an attempt to identify low-risk patients in whom baseline LVEF assessment may not be warranted.

COMMENTARY: Breast cancer therapies have become more targeted and effective in improving patient survival.[1] However, many of these medications have cardiotoxic effects, including reduction in left ventricular ejection fraction (LVEF), arrhythmia, and thromboembolic disease.[2,3] The cardiac effects from chemotherapeutic agents such as anthracyclines have been well studied and have been shown to result primarily from myocyte death, which can cause irreversible LV dysfunction and result in congestive heart failure.[4] Newer agents such as HER2-targeted therapies have been shown to cause a more rapid reduction in LVEF, which is suggested to result from a reversible myocyte dysfunction.[5] Therefore, while the common cardiotoxic effect of many cancer therapies appears to be LV dysfunction, the properties, course and risk factors of these effects may significantly vary based on the type of therapeutic agent.

Consistent with this demonstrated cardiotoxic effect, epidemiologic studies have an increased cardiovascular-related mortality in breast cancer patients receiving chemotherapy.[6,7] As a result, despite improvements in breast cancer therapies, cardiotoxicity has presented a significant barrier to optimal cancer treatment. Substantial research efforts have been made to identify preventive strategies and employing appropriate cardiac monitoring. Current strategies primarily focus on routine LVEF assessment using ECHO, MUGA, or cardiac magnetic resonance imaging.[8] However, although routine LVEF testing is commonly performed peritherapeutically in clinical practice, the utility of this surveillance has been inadequately assessed.[3]

It is in this context that the meta-analysis by O'Brien et al assessed the value of routine MUGA and ECHO prior to starting anthracycline-based adjuvant chemotherapy.[9] Their data suggest that only a small portion of patients in the analyzed observational studies had abnormal LVEF, and an even smaller portion of these patients had changes in their clinical course based on this routine cardiac assessment. Therefore, widespread cardiac function evaluation prior to starting anthracycline-based adjuvant chemotherapy may not represent an efficient and cost-effective strategy for identifying those at risk of developing cardiotoxicity.

The retrospective cohort study by Rushton et al similarly provides interesting findings on the impact of routine cardiac monitoring in breast cancer patients receiving trastuzumab adjuvant therapy.[10] Their study demonstrated lower 5-year OS in patients who did not complete trastuzumab therapy due to symptomatic cardiotoxicity or changes in cardiac parameters on routine imaging, as compared to those who completed 17 cycles of therapy. These results suggest that, although iatrogenic cardiac dysfunction from trastuzumab represents a significant clinical issue, discontinuation of breast cancer treatment may ultimately result in worse survival outcomes. While it is possible that the patient group with cardiotoxicity had higher rates of associated cardiovascular symptoms than were reported in this abstract, results from this study particularly emphasize the need to reconsider the discontinuation of treatment in asymptomatic patients solely based on cardiac parameter changes on imaging. Currently, there are inadequate survival outcome

IN BRIEF

Already known

- Adjuvant anthracycline-based chemotherapy and trastuzumab are beneficial in early-stage breast cancer, but entail a risk of cardiotoxicity.
- Cardiac imaging is used routinely to assess risk of cardiotoxicity in these patients.

What these studies showed

- Trastuzumab: Retrospective analysis found a significant number of patients stopped before recommended 18 cycles following cardiac imaging, but never experienced cardiotoxicity. Disease-free and overall survival was worse in those receiving ≤17 cycles.
- Anthracyclines: Meta-analysis found low overall rates of abnormal cardiac imaging (2.5%) that infrequently affected clinical management (1.6%).

Next steps

- Consider strategies to enable patients to continue therapy following abnormal cardiac imaging.
- Question the widespread use of cardiac function evaluation prior to starting these therapies.

data on patients who continue on cancer treatment in the face of cardiotoxicity, as compared to those who discontinue therapy.

The 2 presentations at the 2018 CAMO conference raise important considerations for balancing the cardiotoxicity of cancer therapies with their survival benefits. Although declining cardiac function can be a cause for concern, it appears that routine monitoring and consequent termination of cancer therapy may not only place a significant financial burden on our healthcare system, but may also reduce OS.[11] Further complicating this issue is a lack of consensus on defining what is considered significant cardiac dysfunction, as well as insufficient data to effectively tailor prevention, monitoring and management of cardiotoxicity to different cancer therapies and patient populations.[3] Without well-defined guidelines at this time, oncologists are faced with the challenge of deciding whether to continue therapy. Overall, these results suggest that, although cardiotoxicity represents a valid and important concern, further research integrating the subfield of cardio-oncology is needed to determine efficient and effective monitoring and decision making.

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