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Original Research

Capecitabine in early breast cancer: A meta-analysis of randomised controlled trials

Akina Natori [a,b], Josee-Lyne Ethier [a,b], Eitan Amir [a,b], David W. Cescon [a,b,*]

[a] *Department of Medical Oncology and Hematology, Princess Margaret Cancer Centre, University Health Network, 610 University Avenue, Toronto, Ontario, M5G 2M9, Canada*

[b] *Division of Medical Oncology and Hematology, Department of Medicine, University of Toronto, 200 Elizabeth Street, Suite RFE3-805, Toronto, Ontario, M5G 2C4, Canada*

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Abstract ***Purpose:*** Capecitabine is an effective therapy for metastatic breast cancer. Its role in early breast cancer is uncertain due to conflicting data from randomised controlled trials (RCTs).
Methods: PubMed and major conference proceedings were searched to identify RCTs comparing standard chemotherapy with or without capecitabine in the neoadjuvant or adjuvant setting. Hazard ratios (HRs) for disease-free survival (DFS) and overall survival (OS), as well as odds ratios (ORs) for toxicities were extracted or calculated and pooled in a meta-analysis. Subgroup analysis compared triple-negative breast cancer (TNBC) to non-TNBC and whether capecitabine was given in addition to or in place of standard chemotherapy. Meta-regression was used to explore the influence of TNBC on OS.
Results: Eight studies comprising 9302 patients were included. In unselected patients, capecitabine did not influence DFS (hazard ratio [HR] 0.99, $p = 0.93$) or OS (HR 0.90, $p = 0.36$). There was a significant difference in DFS when capecitabine was given in addition to standard treatment compared with in place of standard treatment (HR 0.92 versus 1.62, interaction $p = 0.002$). Addition of capecitabine to standard chemotherapy was associated with significantly improved DFS in TNBC versus non-TNBC (HR 0.72 versus 1.01, interaction $p = 0.02$). Meta-regression showed that adding capecitabine to standard chemotherapy was associated with improved OS in studies with higher proportions of patients with TNBC ($R = -0.967$, $p = 0.007$). Capecitabine increased grade 3/4 diarrhoea (odds ratio [OR] 2.33, $p < 0.001$) and hand-foot syndrome (OR 8.08, $p < 0.001$), and resulted in more frequent treatment discontinuation (OR 3.80, $p < 0.001$).

* *Corresponding author*: University Health Network, Princess Margaret Cancer Centre, 610 University Avenue, Toronto, Ontario, M5G 2M9, Canada. Fax: +1 (416) 946 6546.
E-mail addresses: Akina.Natori@uhn.ca (A. Natori), Josee-Lyne.Ethier@uhn.ca (J.-L. Ethier), Eitan.Amir@uhn.ca (E. Amir), dave.cescon@uhn.ca (D.W. Cescon).

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Conclusion: Adding capecitabine to standard chemotherapy appears to improve DFS and OS in TNBC, but increases adverse events in keeping with its known toxicity profile.

1. Introduction

Adjuvant chemotherapy improves survival in early breast cancer. Over the last several decades, enormous investment in large clinical trials has refined treatment regimens to maximise the effectiveness of this therapy. Several large randomised trials (RCTs) have demonstrated that addition of a taxane to anthracycline-based regimens reduces recurrence risk and improves disease-free (DFS) and overall survival (OS) in patients with node-positive breast cancer [1–4]. Such 'third generation' combination chemotherapy regimens incorporating an anthracycline and taxane have thus become a standard of care for appropriately selected patients with high-risk early breast cancer. However, despite these advances in chemotherapy, the 10-year recurrence rate in these patients remains >20% [5,6], highlighting a clinical need for further improvement, which might be achieved by the addition of other effective drugs.

The paradigm for the development of adjuvant chemotherapy has been to test agents demonstrating activity in metastatic disease. Several drugs, including platinum compounds and capecitabine, have been evaluated as adjuvant therapies, but are not standard of care due to conflicting data and methodologic limitations [7–16]. While some trials have specifically selected patients based on oestrogen receptor (ER) status (e.g. platinum chemotherapy in triple-negative breast cancer[TNBC] [9,10,17], based on preclinical biology and activity in the metastatic setting), this has not been an eligibility criterion for most chemotherapy studies. Subgroup analyses have considered differential benefit of various chemotherapy components based on ER, but apart from the specific benefit of dose-dense therapy in ER-negative breast cancer [18,19], drug selection is generally independent of ER status [6]. Several RCTs comparing capecitabine-containing regimens to standard chemotherapy for early breast cancer have been conducted, and subgroup analyses have suggested that capecitabine may be effective in subgroups of patients [14,15]. A potential benefit of adjuvant capecitabine in TNBC is in contrast to the relatively modest antitumour activity of this agent in the metastatic or neoadjuvant setting for such tumours [20–23].

To further study the utility of adjuvant capecitabine, we performed a meta-analysis of RCTs which evaluated capecitabine-containing regimens in early breast cancer, with particular attention to the TNBC subgroup.

2. Methods

This analysis was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [24].

2.1. Search criteria

Medline (Host: PubMed) was searched for studies published from inception to November 2016 using the MeSH terms (1) breast neoplasm and capecitabine and neoadjuvant therapy, and (2) breast neoplasm and capecitabine and adjuvant therapy. Presentations made at American Society of Clinical Oncology (ASCO) Annual Meetings and San Antonio Breast Cancer Symposium in the last 10 years were also searched manually, and additional studies were identified through reviews of citation lists. Eligible trials comprised those evaluating the clinical efficacy of capecitabine in early breast cancer. We included studies reporting results of RCTs that compared standard chemotherapy with or without capecitabine in the neoadjuvant or adjuvant setting. Standard chemotherapy was defined as cyclophosphamide, methotrexate, and 5-fluorouracil, anthracycline-based regimens or anthracycline/taxane combinations. Only the studies reporting hazard ratios (HRs) for OS or DFS were included in the meta-analysis.

2.2. Data extraction

Two reviewers (AN, DC) evaluated independently all the titles identified by the search strategy. The results were then pooled and all potentially relevant publications were retrieved in full and assessed for eligibility. Disagreement was resolved by consensus. The following information was captured: authors' names, year of publication, eligibility criteria, baseline patient characteristics including tumour and treatment characteristics such as hormone (ER, progesterone receptor) and human epidermal growth factor receptor 2 (HER-2) status and chemotherapy dosing regimens. HR and 95% confidence intervals (CI) for the efficacy measures including OS and DFS were extracted where available. Safety and tolerability measures including treatment-related death, treatment discontinuation without progression and grade 3/4 adverse events (AEs) were also extracted. For studies in which there was more than one