EUROPEAN JOURNAL OF CANCER 45 (2009) 2749–2758

available at www.sciencedirect.com

ScienceDirect

journal homepage: www.ejconline.com

Review

The clinical efficacy of cytotoxic agents in locally advanced or metastatic breast cancer patients pretreated with an anthracycline and a taxane: A systematic review

Jacek Jassem[a], *Christopher Carroll*[b,*], *Sue E. Ward*[b], *Emma Simpson*[b], *Daniel Hind*[b]

[a]*Department of Oncology and Radiotherapy, Medical University of Gdansk, Poland*
[b]*Health Economics and Decision Science, School of Health and Related Research (ScHARR), University of Sheffield, Sheffield, UK*

ARTICLE INFO

Article history:
Received 12 May 2009
Accepted 27 May 2009
Available online 15 July 2009

Keywords:
Review
Breast neoplasms
Neoplasms metastes
Anthracyclines
Taxoids
Survival
Adult
Female
Quality of life

ABSTRACT

Introduction: Currently available evidence does not provide definitive guidance regarding the optimal chemotherapy agents and combinations in anthracycline- and taxane-pretreated advanced breast cancer. We performed a systematic review of controlled clinical trials of the cytotoxic agents currently used for this population in Europe: capecitabine, gemcitabine, vinorelbine, docetaxel, paclitaxel and paclitaxel protein-bound particles.

Method: A systematic review of randomised (RCT) and non-randomised controlled clinical trials (non-RCTs). The primary outcomes of interest were overall survival (OS) and progression-free survival (PFS); secondary outcomes were duration of response (DR), overall response rate (ORR), adverse events and quality of life (QoL). Six electronic databases and grey literature sources were searched; reference tracking was performed on included publications. A narrative synthesis was conducted: heterogeneity of study design and interventions prevented meta-analysis.

Results: No randomised controlled trial (RCT) found any significant differences between any of the regimens in terms of OS. In terms of PFS, only gemcitabine plus vinorelbine performed significantly better than its comparator, vinorelbine alone. For secondary outcomes, only capecitabine plus bevacizumab had a significantly better outcome than its comparator, capecitabine alone, in terms of ORR. A low quality non-RCT found that both capecitabine monotherapy and a combination of capecitabine plus vinorelbine were significantly more effective than vinorelbine alone in terms of OS and ORR. Across all trials, median OS for these patients typically remained less than 16 months.

Conclusion: The quantity and quality of the available evidence regarding the efficacy of the particular chemotherapy regimens in patients with advanced breast cancer pretreated with an anthracycline and a taxane is extremely limited. New effective therapies are sorely needed in this population.

* *Corresponding author:* Tel.: +44 0 114 2220864; fax: +44 0 114 2724095.
E-mail address: c.carroll@shef.ac.uk (C. Carroll).
0959-8049/$ - see front matter
doi:10.1016/j.ejca.2009.05.035

1. Introduction

Chemotherapy constitutes the major treatment option in both early and advanced breast cancer and the most active currently available agents are anthracyclines and taxanes.[1,2] However, both primary and acquired resistance limit the efficacy of chemotherapy in metastatic breast cancer (MBC). Additionally, increased use of anthracyclines and taxanes in adjuvant and neoadjuvant setting restricts their applicability at relapse.[3,4] Until recently, the only cytotoxic agent approved in the USA and Europe in anthracycline- and taxane-pretreated or -resistant tumours was capecitabine. Several other compounds, including gemcitabine, vinorelbine and nanoparticle protein-bound paclitaxel, all administered as either monotherapy or in combination with other cytotoxic agents, have shown some activity in this setting and are used at the physician's discretion.[5,6] Some patients are also treated with paclitaxel or docetaxel, whereas reinstitution of anthracyclines is difficult due to risk of cumulative cardiotoxicity.

As opposed to the use of chemotherapy in neoadjuvant and adjuvant setting, there are very few internationally accepted consensus statements on therapy of MBC.[7,8] In particular, currently available evidence does not allow for definitive guidance regarding the optimal agents or the order they should be administered in anthracycline- and taxane-pretreated or -resistant tumours. To our knowledge, no systematic review of controlled clinical studies has been published assessing the clinical efficacy of chemotherapy regimens for the treatment of MBC in patients who have previously had treatment with an anthracycline and a taxane. This review therefore aims to determine the efficacy of the principal cytotoxic agents currently used in Europe in this setting: capecitabine, gemcitabine, vinorelbine, docetaxel, paclitaxel and paclitaxel protein-bound particles. The primary outcomes of interest were overall survival (OS) and progression-free survival (PFS); secondary outcomes were duration of response (DR), overall response rate (ORR), adverse events and quality of life (QoL).

2. Methods

2.1. Search strategy

This review applied standard systematic review methodology.[9] The aim of the search was the comprehensive retrieval of randomised and non-randomised controlled trials of capecitabine, gemcitabine, vinorelbine, docetaxel, paclitaxel and paclitaxel protein-bound particles in anthracycline and taxane resistant or pretreated patients with locally advanced or metastatic breast cancer. A search was performed for randomised controlled trials (RCTs) using the Cochrane Central Register of Controlled Trials (CENTRAL) and the American Society of Clinical Oncology (ASCO) conference proceedings, and a search for non-randomised controlled trial evidence (non-RCTs) was conducted using the major medicine and health-related electronic bibliographic databases MEDLINE, EMBASE, CINAHL and the Science Citation Index, as well as the ASCO annual meeting proceedings. Sensitive search strategies using free-text and, where available, thesaurus terms were developed to search the databases. Synonyms relating to the agents, including chemical and brand names (e.g. Xeloda for capecitabine) were combined with synonyms relating to the condition (breast cancer). An example of the complete CENTRAL search strategy is reported in Appendix 1. In addition to the terms used in the CENTRAL search, a range of terms were used for the non-randomised controlled trials search that aimed to restrict search results to the specific population, i.e. patients with MBC undergoing therapy, who have been treated previously with two or more lines of chemotherapy. These included: 'third line', 'previously treated', 'after treatment with', 'pre-treated', 'subsequent therapy' and 'relapsed', in order to capture the appropriate evidence base. An example of the complete Medline search strategy is reported in Appendix 2. This strategy was modified as appropriate for use on the other databases searched. These searches were also supplemented by other methods to identify relevant citations: the references of all included studies were screened, and industry experts and the reference lists of relevant reviews were also consulted for additional citations. The screening process applied the same inclusion criteria for both sets of search results.

2.2. Selection of studies and quality assessment

To be included in the review, primary research studies had to satisfy the following criteria: controlled trials (randomised or non-randomised); locally advanced or MBC female patients aged $\geqslant$18 years who had received prior therapy with an anthracycline and a taxane; treatment with capecitabine, gemcitabine, vinorelbine, docetaxel, paclitaxel or paclitaxel protein-bound particles either as monotherapy or in combination with each other or other chemotherapeutic agents; any comparator (e.g. placebo or any drug). The primary outcomes for the review were overall survival (OS) and progression-free survival (PFS); secondary outcomes were duration of response (DR), overall response rate (ORR), toxicity and quality of life (QoL). Date limits were not used on any database in either set of searches. Restriction to English language was applied to the search for RCTs, but otherwise language restrictions were not used on any database. Studies were excluded if they were phase 1 or single-arm studies; if the trial was exclusively conducted in HER2+ patients, or if less than 50% of the trial population had been treated with both an anthracycline and a taxane (thereby reducing the validity of the evidence for this review), or if the intervention was a high-dose chemotherapy regimen.

All citations identified by the search of electronic databases were downloaded into a Reference Manager database and duplicates removed. Titles and abstracts from both searches were assessed against the inclusion criteria by a single reviewer. For quality-control purposes, a double check for appropriate inclusion and exclusion was performed on ten percent of the citations by a second reviewer. In cases where a decision could not be made about inclusion by a reviewer, citations were checked by a second reviewer and disagreements were either resolved by discussion or the full paper was retrieved in order to make a definitive judgement. One reviewer extracted data from the final list of included studies into pre-designed tables, which were piloted on an included study, and appraised the quality of the included studies using a form