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Systematic or Meta-analysis Studies

Second-line single-agent chemotherapy in human epidermal growth factor receptor 2-negative metastatic breast cancer: A systematic review

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ABSTRACT

Background: No 'gold standard' exists for single-agent chemotherapy of human epidermal growth factor receptor 2-negative (HER2-negative) metastatic breast cancer (MBC) in the second-line. The objective of this systematic review is to identify and appraise overall survival (OS), progression-free survival (PFS), time to progression (TTP) and Grade ≥3 adverse event evidence for single-agent chemotherapy in this setting.
Methods: MEDLINE, Embase and the Cochrane Library were searched to October 2013, and PubMed October 2013 to November 2014. Electronic database searches were supplemented with hand searching of reference lists and conferences. Eligible randomised controlled trials (RCTs) employed at least one single-agent chemotherapy treatment, enrolled HER2-negative or unselected MBC patients who had progressed following first-line chemotherapy within the metastatic setting, and reported outcomes of interest for the second-line setting.
Results: Fifty-three RCTs were included in total, with most containing mixed populations by HER2 status and treatment line. Fourteen studies reported data specifically for second- and later-line treatment within the metastatic setting. Median overall survival (OS) in most trials was 8–13 months. Only one trial reported a significant difference between studied interventions in the second-line metastatic setting: nab-paclitaxel ($n = 131$) conferred a statistically significant OS advantage vs. three-weekly paclitaxel ($n = 136$) (median OS 13.0 vs. 10.7 months, respectively; hazard ratio 0.73, $p = 0.024$) and improved overall safety.
Conclusion: One RCT demonstrated significant benefit in this setting in confirmed HER2-negative MBC alongside favourable safety. Treatment line terminology was imprecise. To reliably inform patient treatment decisions, quality-of-life data are needed and precise OS estimation according to underlying patient characteristics.

Introduction

Breast cancer is the most commonly diagnosed cancer and a leading cause of cancer mortality in women in both developed and developing countries. The World Health Organization estimates that more than 508,000 women died of breast cancer in 2011 [1]. Approximately 5–10% of women have metastatic breast cancer (MBC) at diagnosis [2], while a further 20–40% of breast cancer patients will go on to develop MBC [3]. MBC is an incurable disease with a median survival of 2–3 years [4–6]. Therefore, the aims of treatment are palliative: to control symptoms in order to maintain and improve patient quality of life (QoL) and, where possible, prolong survival [4].

MBC is a highly heterogeneous disease varying in tumour presentation and in biological and clinical behaviour. There are several molecular subtypes of MBC. Tumours may vary by hormone receptor status (i.e. oestrogen receptor [ER] and progesterone receptor [PR] status) and human epidermal growth factor receptor 2 [HER2] status [7]. Approximately two-thirds of breast cancer tumours express ER and/or PR receptors [8]. Hormone receptor positive tumours can be further sub-divided into luminal A and luminal B molecular subtypes, with luminal B tumours having a poorer prognosis (median survival 30 vs. 45 months) [6,9]. Treatment options include hormonal therapies and selective oestrogen receptor modulators [8]. About 15–20% of newly diagnosed breast

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cancers over-express HER2 (HER2+) [10–12]. These patients are treated with HER2-targeting agents (e.g. trastuzumab), in combination with hormonal therapy and/or chemotherapy [10–12]. HER2-targeting therapies have been shown to improve survival in patients with MBC [10]. In patients who are HER2-negative, but hormone receptor positive with no extensive and/or symptomatic visceral disease, hormone therapy is the first-line treatment option. In those patients with visceral involvement, chemotherapy is usually the treatment of choice [2,13]. Triple-negative tumours do not express ER, PR and HER2, and for these patients chemotherapy is the main treatment option. According to European Society of Medical Oncology (ESMO) guidelines, there are no standard approaches for triple-negative patients requiring second- or later-line chemotherapy [2]. Beyond the use of HER2 and hormone receptor status to guide treatment, there is currently limited progress. The use of molecular profiles to select appropriate treatment options is the subject of intense research and has great potential, but is likely to be sensitive to the emerging plethora of targeted therapies. Chemotherapy options include anthracyclines (e.g. doxorubicin, epirubicin), taxanes (e.g. docetaxel, nab-paclitaxel, and paclitaxel), vinca alkaloids (e.g. vinorelbine), anti-metabolites (e.g. capecitabine), platinum agents (e.g. cisplatin and carboplatin) and eribulin.

Treatment options for patients with MBC are dependent on several factors including disease burden, earlier treatments, response to and time elapsing since last exposure to earlier therapies, and patient characteristics and preferences [2,13,14]. Due to the heterogeneity of the disease, an individualised approach to the treatment of MBC is considered necessary. Following the failure of first-line therapy for MBC, the chance of response to subsequent therapy is reduced by approximately 50% with each previous regimen received [14]. However, due to the lack of predictive factors for specific agents, in some cases it is possible to see a larger than expected therapeutic benefit in second-line and/or further lines of therapy [15]. Single-agent chemotherapy is the preferred treatment option in patients without severely symptomatic or immediately life-threatening disease [2]. In addition, treatment options in the second- and later-line settings are often limited by drug resistance as a result of earlier exposure to cytotoxic regimens [16]. For example, patients receiving second-line treatment for MBC will often have previously received a taxane and/or anthracycline-based chemotherapy, which may subsequently result in treatment-resistant cases of MBC.

At present there is no 'gold standard' of treatment for MBC [14]. Physicians must rely on clinical trial data to make decisions regarding the most beneficial course of treatment for patients following first-line therapy failure [16]. In this respect, well-designed, objective, randomised controlled trials (RCTs) are fundamental to informing clinical practice. However, the majority of trials tend to focus on the comparison of specific treatments in pre-defined patient populations at a specific phase of disease, and also have relatively short follow-up periods, producing MBC populations that are not representative of those seen in clinical practice [17]. There is therefore a need for physicians to understand the current evidence base for single-agent therapy for HER2-negative MBC second-line treatment.

The present systematic review (SR) was conducted in order to qualitatively synthesise the evidence base for the treatment of MBC and to make recommendations regarding future trials in this setting.

Methods

Search strategy

The present SR was performed in accordance with Cochrane recommendations [18]. A pre-defined SR protocol was produced. The original SR searches were run in the electronic databases of MEDLINE, Embase and The Cochrane Library on 17th September 2012. A subsequent update search in these databases was conducted on 30th October 2013. A further update was performed in PubMed for the period 30th October 2013 to 14th November 2014.

Additionally, the following sources were hand searched: reference lists of included RCTs; studies included in relevant SRs; clinical trials databases; and National Institute for Health and Care Excellence (NICE) technology appraisals, evidence reviews and clinical guidelines relating to chemotherapy treatment in patients with advanced or metastatic breast cancer. The following conference proceedings (2010–2013 inclusive) were searched for trial data without full publications: American Society of Clinical Oncology (ASCO); European Cancer Organisation (ECCO); European Society of Medical Oncology (ESMO); International Society for Pharmacoeconomics and Outcomes Research (ISPOR).

Eligible studies were Phase II or Phase III RCTs. Studies meeting the inclusion criteria were RCTs that had enrolled patients to receive single-agent chemotherapy as a second-line treatment for HER2-negative advanced or metastatic breast cancer. 'Second-line' was defined as patients who had received one prior line of chemotherapy treatment in the advanced or metastatic setting. It was anticipated that RCTs would be retrieved that contained 'mixed-lines' (i.e. combined results for patients treated at first-, second- or third-line, etc.); therefore, any studies containing second-line treated patients were included, and the proportions of second-line treated patients noted. It was also anticipated that some trials would pre-date the period from which HER2 testing began in clinical practice. Therefore, the SR included studies where HER2 status of enrolled patients was not reported, as it anticipated that such studies would contain patients who were HER2-negative (albeit at an unknown proportion). Trials of exclusively HER2+ patients and of patients who were naïve to chemotherapy treatment were excluded.

Comparators

The single-agent comparators for the treatment of MBC included in the SR were: taxanes (paclitaxel, nab-paclitaxel, docetaxel), vinca alkaloids (vinorelbine, vinblastine, vincristine), platinum-based treatments (cisplatin, carboplatin), anthracyclines (doxorubicin, pegylated liposomal doxorubicin [PLD], epirubicin) and other monotherapy (capecitabine, gemcitabine, eribulin, melphelan or cyclophosphamide) vs. any comparator. Nab-paclitaxel is licensed in MBC patients for whom anthracyclines are not suitable, so the anthracyclines included here, doxorubicin, PLD and epirubicin, would not be direct comparators, but are included as they may still be used in second-line therapy.

Topoisomerase inhibitors were not included; amrubicin as it is unlicensed in MBC, and irinotecan because it is unlicensed in breast cancer. Also excluded were hormonal treatments (aromatase inhibitors), marimastat (due to its development having been terminated), tyrosine kinase inhibitors (lapatinib, reatinib, afatinib, BMS-754807, sunitinib, pazopanib, dasatinib) and inhibitors of downstream targets (everolimus, BKM120, BEZ-235, tanespimycin, retaspimycin, AUY922).

Outcome measures

The SR focused on the following efficacy outcomes: overall survival (OS), progression free survival (PFS), and time to progression (TTP). Data for QoL and other patient-reported outcomes were also sought. The following toxicity outcomes were included: withdrawal from treatment due to toxicity, haematological adverse events (AEs), non-haematological AEs, Grade three and four AEs, and mortality.