

Meta-analysis of phase III trials of docetaxel alone or in combination with chemotherapy in metastatic breast cancer

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Abstract

Purpose Whether combination chemotherapy offers an advantage over sequential therapy in metastatic breast cancer (MBC) is still an unsettled issue. Polychemotherapy regimens containing taxanes has been shown to increase overall survival (OS), time to tumor progression (TTP), and overall response rate (ORR) when compared with regimens that did not contain a taxanes, while taxane-based doublets have a statistically significant benefit over single-agent taxane only for progression-free survival. However, the term “taxanes” generally includes both paclitaxel and docetaxel, drugs with different clinical activity. Aim of this work is to compare OS, TTP, and ORR in patients with MBC receiving docetaxel alone or in combination with chemotherapy using a formal meta-analysis.

Methods We performed a systematic review of all published trials comparing docetaxel alone or in combination with other chemotherapeutic agents in MBC.

Results Three randomized clinical trials including 1,313 patients were retrieved. A significant reduction of risk ratio was found in TTP ($P \leq 0.0001$) but not in OS ($P = 0.48$) or ORR ($P = 0.10$) for patients treated with a chemotherapy

agent plus docetaxel compared with docetaxel alone. Treatment with docetaxel alone is associated with a lower incidence of grade 3 diarrhea and stomatitis (diarrhea, $P = 0.011$; stomatitis, $P = 0.0004$).

Conclusion Combination chemotherapy regimens with docetaxel show a statistically significant advantage for TTP, but not for OS and ORR in MBC. This review confirms that it is unlikely that any single agent or combination chemotherapy regimen will emerge as superior in MBC, due to its heterogeneous nature.

Keywords Metastatic breast cancer · Meta-analysis · Docetaxel · Taxanes

Introduction

Metastatic breast cancer (MBC) is still an incurable disease, even if mortality has been decreasing steadily in the developed countries in the last 10 years (Jemal et al. 2010a, b). Approximately 6% of women with breast cancer are metastatic at diagnosis and ~20% of patients initially diagnosed with localized disease will develop MBC (Brewster et al. 2008). Goals of therapy include prolongation of survival, delay of disease progression, and palliation of symptoms.

The medical treatment of MBC includes a wide range of options (chemotherapy, endocrine treatment, and therapy with monoclonal antibodies and tyrosine kinase inhibitors) with chemotherapy still representing the mainstay of treatment (Force 2007; Beslija et al. 2009).

Whether combination chemotherapy offers an advantage over sequential therapy for the management of MBC is still an unsettled issue (Cardoso et al. 2009, 2010; Kostler et al. 2010). A recent review of trials using combination versus

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single-agent chemotherapy in MBC (Carrick et al. 2009) shows a significant advantage of polychemotherapy in terms of overall response rate (ORR), progression-free survival (PFS), and overall survival (OS), but these data are hampered by the use, in several cases, of single agents (such as mitoxantrone, lomustine, ifosamide, etc.) that are no longer considered as standard treatments. Therefore, these findings may not be applicable to more recent active single agents such as taxanes, currently considered as the cornerstones of MBC treatment (Radaideh and Sledge 2008). Also the effects of adding one or more chemotherapy drugs at first-line regimen of at least two chemotherapy drugs have been reported to have a statistically significant advantage for ORR, but no differences in OS or time to tumor progression (TTP) and the positive effect being associated with increased toxicity (Butters et al. 2010).

Polychemotherapy regimens containing taxanes have been shown to increase OS, TTP, and ORR when compared with regimens that did not contain a taxane (Ghersi et al. 2005a, b), even if taxanes in combination with anthracyclines did not show an OS benefit over single-agent taxanes, when used as first-line treatment of MBC (Piccart-Gebhart et al. 2008). The clinical activity of taxane monotherapy against taxanes in combination regimens has been extensively investigated (Cardoso et al. 2009). A recent meta-analysis has shown a statistically significant benefit in favor of taxane-based (paclitaxel or docetaxel) doublets over single-agent taxane only for PFS and a non significant trend toward an improved ORR in patients with advanced breast cancer and prior anthracycline treatment (Xu et al. 2011).

A major problem in interpreting these data is related to the fact that the term “taxanes” generally includes paclitaxel, docetaxel, and nanoparticle albumin-bound paclitaxel (nab-paclitaxel), although they differ with respect to pharmacokinetic profile, toxicity, and clinical activity (Ghersi et al. 2005b; Rosati et al. 2011; Ardavanis et al. 2008; Mukai et al. 2010; Burstein et al. 2007; Jones et al. 2005). Moreover, many published trials allow to use indifferently paclitaxel *or* docetaxel in one arm of treatment (Rosati et al. 2011; Ardavanis et al. 2008; Mukai et al. 2010; Burstein et al. 2007) with docetaxel appearing superior to paclitaxel in most trials doing a direct comparison (Jones et al. 2005; Vu et al. 2008; Lin et al. 2007).

The aim of this work is to compare OS, TTP, and ORR in patients with MBC receiving docetaxel alone or docetaxel in combination with other chemotherapeutic agents using a formal meta-analysis. We performed a comprehensive systematic review of all randomized phase III trials that compared docetaxel alone or in combination with polychemotherapy without the addition of biologics (such as trastuzumab or bevacizumab) in MBC. Three trials corresponded to the above-mentioned characteristics

(O’Shaughnessy et al. 2002; Pacilio et al. 2006; Sparano et al. 2009).

Methods

Data sources and selection criteria

The goal of this study was to determine whether addition of chemotherapy agent(s) to docetaxel monotherapy improves outcome of MBC. We included prospective, randomized, controlled open or blinded trials of participants with metastatic breast cancer.

We excluded non-randomized trials and quasi-randomized trials with alternate allocation of patients; data on other malignancies; trials comparing radiotherapy, hormonal and gene therapy; trials with biological agents; arms comparing local routes of administration; and comparisons of chemotherapy against no treatment (best supportive care).

The outcomes of interest were OS, TTP, ORR, and toxicity

Using the terms related to MBC treated with docetaxel and a filter highly sensitive for randomized controlled trials only, we searched Medline, Cochrane Central, EmBase, and Cancer Lit for articles published in English from January 2000, to December 2010. In addition, we integrated the electronic search with published abstracts from conference proceedings. Two authors independently reviewed results of the search strategies and identified eligible trials; data extraction was done independently by the same authors using a predefined form. Information was collected on study design, study sample, characteristic of the populations, interventions, line of chemotherapy, methodological quality of the trials, and outcomes (OS, TTP, and ORR).

For each trial, we recorded median survival and number of deaths in each arm, wherever available, and whether the trial noted a statistically significant difference in survival between the compared arms (two tailed $P < 0.05$)

Discrepancies between the two reviewers were resolved through discussion and consensus, with an arbitrator.

Quality assessment of methods

Methodological quality of included randomized controlled trials was assessed by several domains: allocation concealment (considered “adequate” if randomization method was described such that it would not allow the investigator or participant to know or influence the intervention group before eligible participants had entered the study; “unclear” if randomization was stated, but no information on method used was available; “inadequate” when the

study used a method of randomization such as alternation, medical record numbers, date of birth, or unsealed envelopes, or if any information in the study indicated that investigators or participants could influence allocation to the experimental or control group); blinding of investigators, participants, and outcome assessors; use of intention to treat analysis; completeness of follow-up.

Discrepancies in data extraction between the two reviewers were resolved by discussion and consensus, with an arbitrator.

Statistical analysis

We compared treatments using relative risks with 95% confidence intervals. Heterogeneity between studies was assessed with the Cochran’s Q and the I² statistics (Higgins et al. 2003). The pooled risk ratio (RR) estimate was calculated using random-effect model (van Houwelingen et al. 2002). To statistically assess any publication bias, we used the Egger regression asymmetric test, with a .05 level of significance (Egger et al. 1997). The influence of potential sources of heterogeneity on treatment effects was explored by subgroup analysis. The following characteristics of the population, intervention, and methodological quality of the trials were defined a priori as potential effect modifiers: duration of treatment, allocation concealment, and compliance with treatment. Analyses were carried out using a macro routine written in SAS Language (Release 9.1, 2002–2003).

Results

Study characteristics

Of 217 potentially eligible studies identified by the search strategy, 164 were excluded because they tested an intervention other than docetaxel monotherapy versus docetaxel in combination with chemotherapy and 50 because they were not randomized controlled trials, or did not assess OS, TTP, or ORR.

A total of 3 trials (O’Shaughnessy et al. 2002; Pacilio et al. 2006; Sparano et al. 2009) were assessed in full text. Tables 1 and 2 outline the main characteristics of interventions and outcomes of included randomized clinical trials. The trials were published between 2002 and 2009 and carried out in USA and Italy.

All the selected studies enrolled patients pretreated with anthracyclines in different settings (i.e., adjuvant, neoadjuvant, or metastatic). O’Shaughnessy et al. (2002) report significantly superior TTP and OS achieved with the addition of capecitabine to docetaxel in 511 patients progressing after anthracycline treatment either in the (neo) adjuvant or the metastatic setting. Two studies enrolled patients treated with anthracyclines in the adjuvant–neoadjuvant setting, with docetaxel administered as first- or second-line therapy for the metastatic disease. Pacilio et al. (2006) randomized 51 metastatic breast cancer patients, pretreated with adjuvant–neoadjuvant epirubicin, to docetaxel plus epirubicin versus docetaxel alone as first-line

Table 1 Characteristics of interventions of selected clinical trials

Features	O’Shaughnessy et al. (2002)	Pacilio et al. (2006)	Sparano et al. (2009)
Country	USA	Italy	USA
Study design	Randomized	Randomized	Randomized
Primary end point	TTP	ORR	TTP
Secondary end points	OS, ORR	OS, TTP	OS, ORR
Treatment	Capecitabine 1,250 mg/m ² twice daily on days 1 to 14 and docetaxel 75 mg/m ² on day 1 or docetaxel 100 mg/m ² on day 1. Cycles repeated every 21 days.	Epirubicin 75 mg/m ² and docetaxel 80 mg/m ² or docetaxel 100 mg/m ² on day 1. Cycles repeated every 21 days.	Pegylated liposomal doxorubicin 30 mg/m ² and docetaxel 60 mg/m ² on day 1 or docetaxel 75 mg/m ² on day 1. Cycles repeated every 21 days.
Setting	Anthracycline-pretreated metastatic breast cancer	Anthracycline pretreated in the neoadjuvant/adjuvant setting. No previous chemotherapy for metastatic breast cancer	Anthracycline pretreated in the neoadjuvant/adjuvant setting. Prior hormonal treatment and/or one regimen of chemotherapy for metastatic disease were acceptable

Table 2 Outcomes in selected clinical trials

Features	O'Shaughnessy et al. (2002)		Pacilio et al. (2006)		Sparano et al. (2009)	
	Combo	Mono	Combo	Mono	Combo	Mono
No. of patients	255	256	26	25	373	378
OS, median (months)	14.5	11.5	18.0	21.0	20.5	20.6
TTP, median (months)	6.1	4.2	9.0	11.0	9.8	7.0
ORR (%)	42	30	72 ^a	79 ^a	35	26
Complete response (%)	5	4	16	25	–	–
Partial response (%)	–	–	56	54	–	–
Stable disease (%)	38	44	16	12	–	–
Progressive disease (%)	11	20	12	4	–	–
Not assessable (%)	10	6	–	4	–	–

^a Not eligible = 4% of patients, ORR on % of eligible patients. Combo: combination arm with docetaxel; Mono: docetaxel single agent

therapy. The study indicates that the addition of epirubicin to docetaxel does not improve PFS and OS as compared to single-agent docetaxel, but a major limitation of these data is that enrollment has been stopped earlier than planned due to poor accrual (Pacilio et al. 2006). Sparano et al. (2009) enrolled MBC patients, previously treated with neoadjuvant–adjuvant anthracycline therapy. Prior hormonal treatment of advanced breast cancer and/or one regimen of chemotherapy for advanced metastatic disease, excluding anthracycline, paclitaxel, docetaxel, vinorelbine, or vinblastine, were accepted. Seven hundred and fifty-one patients were randomly assigned to receive either docetaxel alone or docetaxel plus pegylated liposomal doxorubicin (PLD). Treatment with PLD–docetaxel significantly improved TTP and ORR, but not OS (Sparano et al. 2009).

In total, these three trials enrolled 1,313 patients: 654 of them received docetaxel combinations and 659 docetaxel as a single agent.

Quality assessment

Based on current standards, the quality of the included studies was suboptimal. Allocation concealment was adequately described in two of the three studies (O'Shaughnessy et al. 2002; Pacilio et al. 2006) and unclear in the remainder (Sparano et al. 2009).

All the studies adequately described blinding of outcome assessors and the others domains. One of these was interrupted earlier (Pacilio et al. 2006).

Clinical outcomes

No significant benefit in OS was found with a chemotherapy agent plus docetaxel compared with docetaxel alone (RR: 0.92, 0.73–1.16; $P = 0.48$). Heterogeneity among the studies in this analysis was moderate ($Q = 4.68$; $P = 0.096$; $I^2 = 57.24\%$; Fig. 1).

A significant reduction in risk ratio was found in TTP with chemotherapy agent plus docetaxel compared with docetaxel alone (RR: 0.66, 0.58–0.74; $P = <0.0001$). Heterogeneity was not significant among studies in this analysis ($Q = 1.46$; $P = 0.48$; $I^2 = 0\%$; Fig. 1).

Regarding ORR, polychemotherapy did not increase the probability of response (RR: 1.22, 0.96–1.56; $P = 0.10$) as compared with docetaxel alone. Heterogeneity in this analysis was moderate ($Q = 5.12$; $P = 0.077$; $I^2 = 60.93\%$; Fig. 2).

Toxicity

Figure 3 presents the summary estimates of the toxicity of chemotherapy agent plus docetaxel compared with docetaxel alone. Results show that a treatment with docetaxel alone is associated with a lower incidence of grade 3 neutropenic fever, nausea, neutropenia, diarrhea, and stomatitis, although only for diarrhea and stomatitis, the results have statistical significance (diarrhea, RR: 2.51, 1.45–4.34; $P = 0.011$; stomatitis, RR: 5.62, 2.16–14.63; $P = 0.0004$).

Heterogeneity among the studies in this analysis was not significant regarding diarrhea ($Q = 0.70$; $P = 0.70$; $I^2 = 0\%$), and moderate relative to stomatitis ($Q = 3.66$; $P = 0.16$; $I^2 = 45.35\%$).

Discussion

The efficacy of docetaxel in MBC has been mostly established in randomized phase III trials (Chan et al. 1999; Nabholz et al. 1999, 2003; Mackey et al. 2002) designed to test chemotherapy with docetaxel versus chemotherapy without docetaxel. This is the first meta-analysis of prospective studies (O'Shaughnessy et al. 2002; Pacilio et al. 2006; Sparano et al. 2009) addressing the question of whether the addition of chemotherapy agents to single-

Fig. 1 Overall survival and time to tumor progression risk ratios

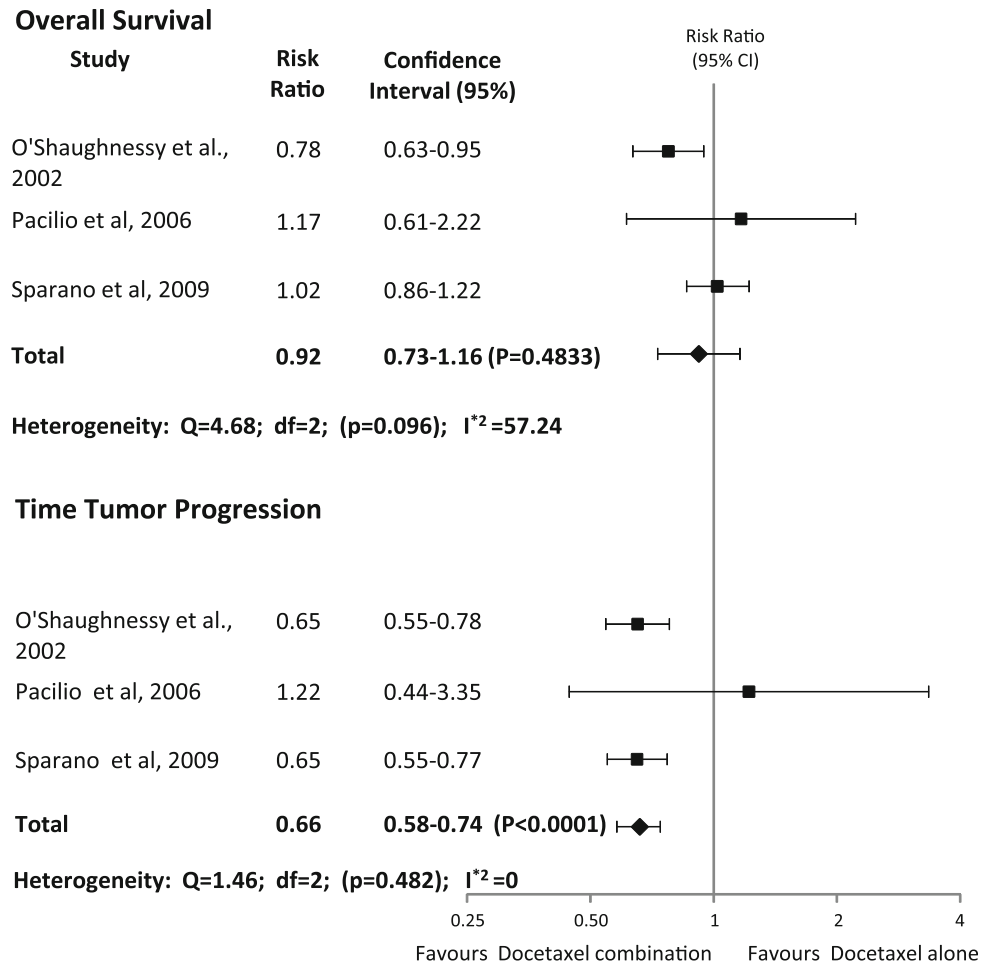


Fig. 2 Overall response rate risk ratios

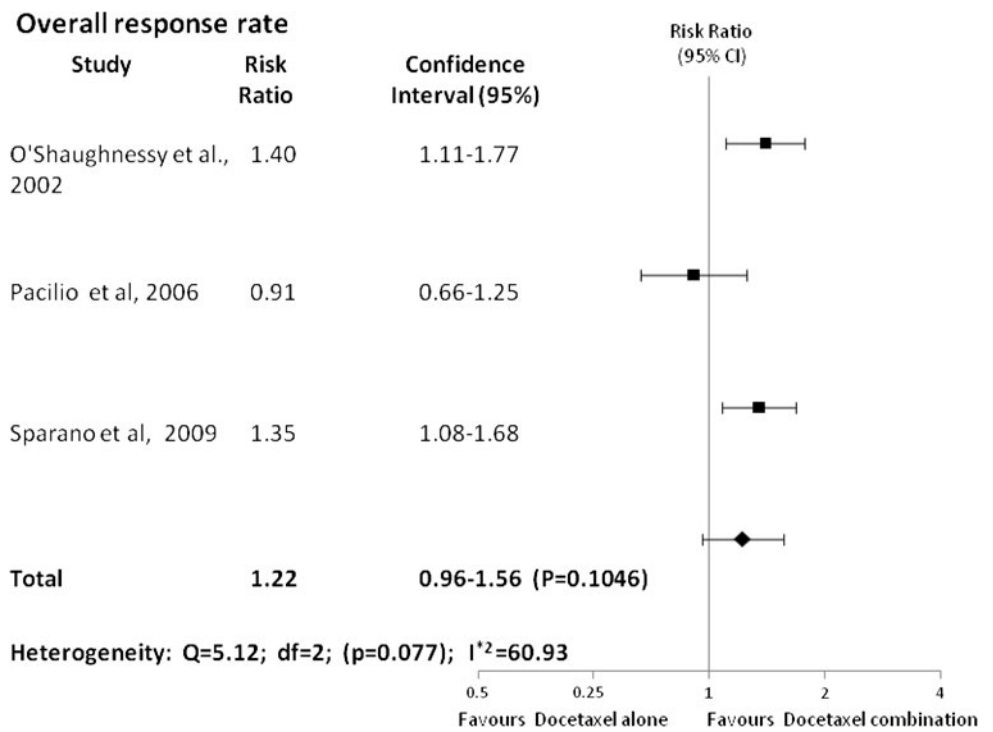
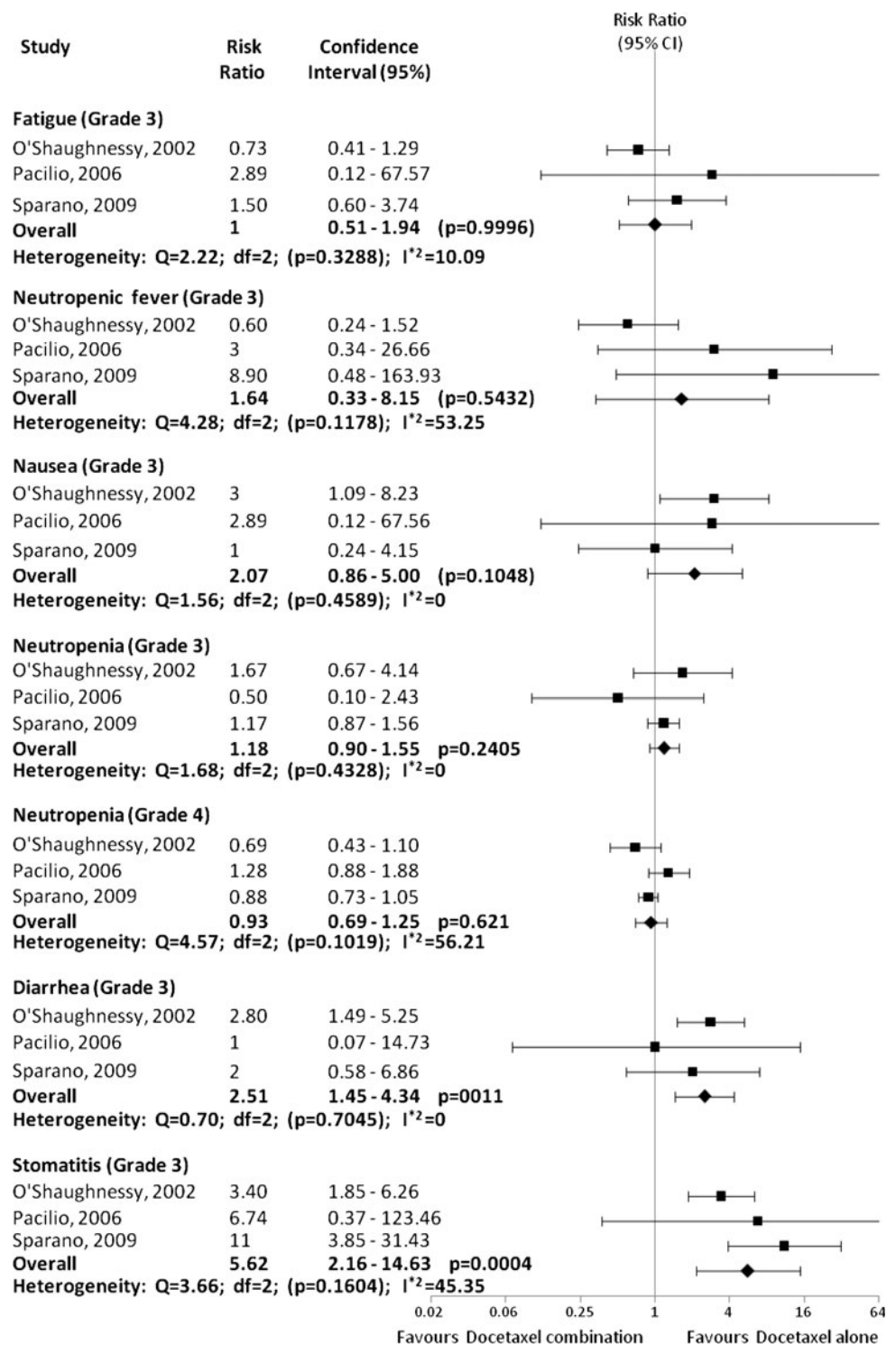


Fig. 3 G3 and G4 toxicity risk ratio

agent docetaxel improves outcome in MBC. In our analysis, combination chemotherapy with docetaxel demonstrated a significant reduction in the risk of TTP as compared with docetaxel alone, but not a clear benefit in terms of either OS or ORR. The lack of significance in OS can be explained by the fact that all the studies were underpowered to detect a benefit in survival, even if

O'Shaughnessy et al. (2002) found a significant advantage in favor of the combination arm. Also, the absence of a significant benefit for polychemotherapy in terms of ORR may be attributed to the limited number of patients included in the study by Pacilio et al. (2006), which was early terminated due to poor accrual and accounts for most of the observed heterogeneity.

Heterogeneity among trials was also related to different schedules, selection of patients, and line of treatment. Docetaxel in monotherapy was used at the dose of 100 mg/m² by O'Shaughnessy et al. (2002) and by Pacilio et al. (2006), and at the dose of 75 mg/m² by Sparano et al. (2009), always administered at day 1 with cycles repeated every 21 days. All enrolled patients have been previously treated with anthracyclines, either in the metastatic setting (O'Shaughnessy et al. 2002) or in the neoadjuvant/adjuvant setting (Pacilio et al. 2006; Sparano et al. 2009). Only the study by Pacilio et al. enrolled patients who did not have previous chemotherapy for metastatic breast cancer, while for O'Shaughnessy et al. (2002), patients with breast cancer in progression during/after anthracycline treatment for metastatic disease or relapsing within 2 years of completing (neo) adjuvant anthracycline-based chemotherapy, were eligible. In the study by Sparano et al. (2009), prior hormonal treatment of advanced breast cancer and/or one regimen of chemotherapy for advanced metastatic disease were acceptable, but treatment of the advanced disease with an anthracycline, paclitaxel, docetaxel, vinorelbine, or vinblastine was not allowed. In two studies, docetaxel was used in combination with anthracyclines, epirubicin (Pacilio et al. 2006), or pegylated liposomal doxorubicin (Sparano et al. 2009), and in the last study in combination with the oral fluoropyrimidine capecitabine (O'Shaughnessy et al. 2002).

No significant difference between docetaxel in combination therapy versus single-agent docetaxel has been found in the evaluable patient population for toxic effects such as fatigue, nausea, neutropenic fever, and neutropenia. Only grade 3 diarrhea and stomatitis had a higher statistical incidence in the combination arms.

Our data confirm results obtained by Xu et al. (2011), who explored through a literature-based meta-analysis whether taxane-based doublets improve outcome over single-agent taxane in patients with MBC. They show that docetaxel- or paclitaxel-based doublets appear to improve PFS, but not OS and ORR with grade 3–4 stomatitis and diarrhea, significantly higher in taxane-based doublets. Even if OS has also been shown to be an elusive end point and questioned, since it may be influenced by imbalance in use of active second-line therapies, by frequent cross-over to the investigational agent(s), and by the fact that many randomized trials are underpowered to detect OS differences, a formal validation of PFS or TTP as a surrogate for OS has so far been unsuccessful in MBC (Saad et al. 2010; Di Leo et al. 2004; Burzykowski et al. 2008).

Our meta-analysis shows that with available data from randomized clinical trial, we are still unable to clearly set the role of docetaxel in the treatment of MBC, thus the single drug versus combination regimens controversy still persists. The strength of this investigation is that it

represents a comprehensive review, based on a predefined study protocol and rigid inclusion criteria for randomized trials only. The main weakness is represented by the paucity of high-quality randomized trials testing this issue, and it is not based on individual patient data. In addition, heterogeneity between trials was found in some analyses, and causes of heterogeneity could not be explored owing to the scarcity of data.

In conclusion, combination chemotherapy regimens with docetaxel versus single-agent docetaxel show a statistically significant advantage for TTP, but not for OS and ORR in women with MBC, but they also produce more toxicity in terms of diarrhea and stomatitis. The results and limitations of this review confirm that it seems unlikely that any single agent or combination regimen will emerge as superior in all patients with MBC, most probably due to the highly heterogeneous nature of this disease (Perou et al. 2000; Sorlie et al. 2001; Wirapati et al. 2008).

Conflict of interest None of the authors has any potential financial conflict of interest related to this manuscript.

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