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ANTI-TUMOUR TREATMENT

Overall survival benefit for weekly vs. three-weekly taxanes regimens in advanced breast cancer: A meta-analysis

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SUMMARY

Background: Taxanes have been extensively tested in patients with advanced breast cancer, but it is unclear whether their weekly use might offer any benefits against standard every three weeks administration. We therefore performed a meta-analysis of randomized controlled trials that compared weekly and every three weeks taxanes regimens in advanced breast cancer.
Methods: The endpoints that we assessed were objective response rate, progression free survival (PFS) and overall survival. Efficacy data for paclitaxel and docetaxel were separately analyzed. Trials were located through PubMed and Cochrane Library searches and abstracts of major international conferences.
Results: Objective response rate was notably better when paclitaxel was used as every three weeks regimen (7 studies, 1772 patients, fixed effect model pooled RR 1.20 95%CI 1.08–1.32 $p < 0.001$). No difference were found for PFS (6 studies, 1610 patients, random effect model HR 1.02, 95%CI 0.81–1.30 $p = 0.860$); while OS was statistically higher among patients receiving weekly paclitaxel (5 studies, 1471 patients, fixed effect model pooled HR 0.78, 95%CI 0.67–0.89 $p = 0.001$). No differences were observed for the weekly compared to the every three weeks use of docetaxel either for objective response, PFS and OS. Overall, the incidence of serious adverse events, neutropenia, neutropenic fever, and peripheral neuropathy were significantly lower in weekly taxanes schedules. The incidence of nail changes and epiphora were significantly lower in the every three weeks docetaxel regimens.
Conclusions: Use of paclitaxel in weekly regimen give overall survival advantages compared with the standard every three weeks regimen. The observed survival benefit does not seem to stem from an increased potency of the drug with weekly regimens. The use of weekly paclitaxel regimens is therefore recommended for the treatment of locally advanced/metastatic breast cancer.

Introduction

Chemotherapy is the cornerstone of therapy for patients with hormone-receptor negative metastatic breast cancer. Anthracyclines and taxanes seem to be the most active agents and various combinations have been tested for optimisation of the results.[1]

In an attempt to improve therapeutic efficacy and toxicity profile of taxanes various phase I and II studies have been conducted with weekly administration of the regimen in various malignancies, including breast cancer.[2–5] It seemed that this schedule had a favourable toxicity profile with encouraging response rates.

Hence randomized trials were developed to compare the weekly vs. three-weekly schedule. We therefore conducted a systematic review of the literature and meta-analysis in order to compare overall survival, progression free survival (PFS) and objective response in patients receiving weekly taxanes versus three-weekly taxanes, for patients with metastatic or locally advanced breast cancer. Since schedule of administration might have a different impact according to the taxane used, paclitaxel and docetaxel efficacy data were separately analyzed.

Materials and methods

Identification of randomized studies

We searched MEDLINE and the CochraneCentral Register of Controlled Trials, without year and language restriction. We used *(mammary OR breast) AND (cancer OR malign* OR neoplas**

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OR carcinom) AND (docetaxel OR paclitaxel OR nab-paclitaxel OR albumin-bound paclitaxel OR taxanes)* as searching algorithm. The last search was updated in January 2009. On the basis of the title and abstract, we downloaded or requested full articles. Reference lists in these trials were checked to identify any other published or unpublished data. We hand-searched the references of review articles and evaluated symposia proceedings, poster presentations, and abstracts from major cancer meetings (including American Society of Clinical Oncology Annual meetings, San Antonio Breast Cancer Symposium, European Society of Medical Oncology and European CanCer Organisation Congress). We also searched the contents of Annals of Oncology, Journal of Clinical Oncology and European Journal of Cancer. Cross-searches were performed in MEDLINE using the names of investigators who were lead authors in at least one eligible trial. In cases that essential data for the analysis were missing personal contact with the corresponding author was attempted.

Study selection

Abstracts, full articles, and the grey literature that passed the primary screening were retrieved and scrutinized. For inclusion, an article had to report a randomized controlled trial. We considered eligible all randomized controlled trials comparing weekly and three-weekly taxanes in patients with advanced breast cancer. Due to the different characteristics of different taxane drugs, the same taxane compound should have been used between the compared arms. If multiple publications of the same trial were retrieved or if there was a case mix between publications, only the most recent publication (the most informative) was included.

Nonrandomized studies were excluded, as were case reports, letters, editorials, commentaries, reviews, and abstracts with insufficient details to meet the inclusion criteria.

Data extraction and outcomes

From each eligible trial we recorded for both arms the following items: authors' name, journal and year of publication, country of origin, years of patient enrolment, and number of centers involved; number of patients randomized and analyzed per arm, age, weight, ER/PR and HER2 status, median follow up and prior therapy.

Main outcome measures were recorded and included number of patient deaths, time until disease progression, number of objective response and number of clinical benefit. Secondary outcome included number of patient with adverse events that reported in two or more eligible trials.

For efficacy analyses data of docetaxel and paclitaxel were separately analyzed. Furthermore since the study design was different in many cases with dissimilar drug combinations or administration schedule, both overall analyses and subgroup analyses for study design were performed.

For toxicity analyses only studies with similar study design (single agent vs. single agent) were included.

Statistics

Two-by-two tables were constructed and odds ratio (OR) was calculated for each primary study to estimate the relative risk of overall response in patients with advanced breast cancer receiving weekly versus tri-weekly taxanes. For each eligible study group, we estimated the relative risk for the overall response rate between the groups in comparison and the 95% confidence interval (CI).

For time-to-event outcomes (overall survival and PFS), when Hazard Ratios were not immediately available from the primary report, they were calculated using Tierney methodology.[6]

We then synthesized the data across studies using fixed effects (Mantel–Haenszel) or random effects (DerSimonian and Laird) modeling when between-study heterogeneity was present.[7] A random effects model assumes that each study has it's own true effect size, whereas a fixed effects model assumes that there is only one true effect size. Since, most studies presented differences in clinical design and methodology, we preferred a random effects model. The presence of statistical heterogeneity was assessed with Cochran's Q test (considered significant for $p < 0.10$)[8] and quantified using I^2 and respective 95% confidence intervals.[9] For I^2 values $\geqslant 50\%$ indicate large heterogeneity and values $\geqslant 75\%$ indicate very large (extreme) heterogeneity.[10] Finally, we synthesized separately studies based on the type of comparative chemotherapy treatment used, e.g. taxanes. Analyses were performed in STATA SE 10.0 (Stata Corp, College Station, TX). All p-values are two-tailed.

Results

Electronic search yielded 4644 hits from PubMed and 658 from Cochrane. In all 11 eligible randomized trials were retrieved, six from peer reviewed report[11–16] and five from congress abstracts.[17–21] Two old studies presented as abstracts reported at ASCO 2002 remained still unpublished in 2009.[17,20] One study retrieved in abstract conference[18] was published in peer-reviewed journal after electronic searches and data freeze,[22] adjourned data were included in the analyses.

In all, 11 eligible trials pertaining $n = 2540$ patients were included in the meta-analysis. Data on 2254 patients were eligible for analyses; of those 1065 patients had been randomized to weekly taxanes regimens, and 1074 to every three week taxanes regimens.

Characteristics of the studies

Study design was not homogeneous across different studies. Among the comparisons eligible for analysis four were pertaining docetaxel,[11,12,17,21] six paclitaxel[13–16,19,20] and one nab-paclitaxel.[18] Six studies presented similar design and compared the use of single agent weekly taxanes with single agent every three weeks taxanes.[11–13,17,18,21] Comparison among docetaxel regimens pertained four of these studies.[11,12,17,21] In one study pertained only locally advanced breast cancer patient were randomized,[15] while the other studies pertained to metastatic disease.[11–14,16–21] In one study[14] single agent weekly paclitaxel was compared to combined chemotherapy with every three week paclitaxel. In Frasci reports weekly combinational chemotherapy with three drugs were compared to every three week chemotherapy with two drugs.[15,19] Intermediate conditions analyzing split taxanes dosage (D1, D8 every three weeks) as a surrogate of weekly regimen (vs. classical every three weeks)[16] or of the every three week regimen (vs. classical weekly)[20] was found in two reports.[16,20] Table 1 shows the key characteristics of the 11 included studies. In one eligible study[21] no data were available for analyses.

In one of the studies two investigational arms and one control arm were available for survival analyses.[18] In this trial patients were randomized to the investigational weekly arms received nab-paclitaxel in two different doses, 100 mg/m^2 or 150 mg/m^2. Since hazard ratios for OS and PFS were available separately for the two dosage of weekly nab-paclitaxel, to avoid double counting of placebo arm, only data from the investigational arm with weekly dosage of 150 mg/m^2 were included in the meta-analyses for OS. The choice was driven by the fact that the dose intensity ratio of nab-paclitaxel used in the investigational and control arms (150 mg/m^2 weekly vs. 300 mg/m^2 every three weeks) was similar to the dose intensity ratio used for paclitaxel (80 mg/m^2 weekly vs.