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Head-to-head: docetaxel challenges paclitaxel

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Among the novel chemotherapeutic drugs introduced in the 1990s, the taxoids have emerged as the most powerful compounds in metastatic breast cancer. For a number of years, clinical trials have investigated the efficacy of the two taxoids, docetaxel (Taxotere®) and paclitaxel (Taxol®), and oncologists have long asked the question whether the two agents are clinically different. However, until this time, only indirect clinical comparisons of these agents had been performed, which were imprecise owing to differences in patient populations. The TAX 311 study is the first and only head-to-head randomised phase III study to compare directly the efficacy and safety of docetaxel and paclitaxel for patients with advanced breast cancer. An early study in patients with paclitaxel-resistant breast cancer revealed differences between the taxoids and now, with the results of the newly published TAX 311 trial, it is possible to make a definitive comparison of docetaxel and paclitaxel.

As previously mentioned, paclitaxel was isolated from the bark of the Pacific yew tree (*Taxus brevifolia*) and docetaxel was, some years later, prepared from 10-deacetyl-baccatin III, isolated from the needles of the European yew tree (*Taxus baccata*) [1]. Despite both compounds being members of the same class of cytotoxic agent, preclinical studies demonstrated that docetaxel had a number of advantages over paclitaxel. Compared with paclitaxel, docetaxel had a wider cell-cycle activity and demonstrated a greater affinity for the β-tubulin binding site [2]. These effects were accompanied by greater uptake and slower efflux of docetaxel from tumour cells, resulting in longer intracellular retention time and higher intracellular concentrations than those achieved with paclitaxel [3]. Compared with paclitaxel, docetaxel demonstrated more potent induction of *bcl-2* phosphorylation and exhibited up to a 12-fold increase in cytotoxic activity [2,4–6]. Also, growth inhibition in human epidermal growth factor receptor 2 (HER2)-positive cells was greater for docetaxel than for paclitaxel [7]. Lastly, the increased upregulation of thymidine phosphorylase observed with docetaxel and capecitabine resulted in a synergistic effect of this combination and a subsequent enhanced cytotoxicity compared with a paclitaxel-containing combination [8].

In order to assess whether these preclinical differences between the taxoids would translate into differences in the clinical setting, we conducted a phase II trial to establish the role of docetaxel in paclitaxel-resistant breast cancer, the results of which were published in the *Journal of Clinical Oncology* in 1998 [9]. Forty-six patients whose cancers were resistant to paclitaxel were given full-dose docetaxel (100 mg/m^2) every 3 weeks. In the 44 patients who were evaluable, the overall response rate (ORR) was 18%, but this was increased to 25% in patients who had been previously treated with paclitaxel in 1- to 3-hour infusions. These results suggested that prior treatment with paclitaxel did not appear to reduce the response rate and demonstrated that docetaxel is active in patients with paclitaxel-resistant breast cancer. As such, these data confirmed the findings of preclinical experiments that indicated only partial cross-resistance between paclitaxel and docetaxel, and provided the first evidence that docetaxel was clinically different from paclitaxel.

A number of studies have further investigated the differences between the taxoids, but as these trials did not directly compare the taxoids, it was not possible to draw any concrete conclusions from a comparison of their findings. It is only recently that the results of the only head-to-head comparison of docetaxel and paclitaxel have become available. The TAX 311 study was published in the *Journal of Clinical Oncology* on 20 August 2005, and is the only randomised phase III study to compare directly the efficacy and safety of docetaxel and paclitaxel as monotherapy for patients with advanced breast cancer who had progressed on prior anthracycline therapy [10]. In this large study, conducted primarily in North America and Canada, the majority of patients had measurable bidimensional metastatic disease, although a small percentage had locally advanced breast cancer. Patients had received an anthracycline (doxorubicin) as adjuvant therapy and prior hormone therapy was allowed, but prior therapy with a taxoid was an exclusion criterion.

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Eligible patients were randomised to receive the Food and Drug Administration (FDA) and European Agency for the Evaluation of Medicinal Products (EMEA) approved dose of either docetaxel (100 mg/m^2; $n=225$) or paclitaxel (175 mg/m^2; $n=224$). Both regimens were administered as 3-weekly schedules until disease progression. No prophylactic growth factors or antibiotics were permitted, although dose reductions were allowed to manage treatment-related toxicity. The treatment arms were well balanced for patient and tumour characteristics, with no statistically significant differences between the two arms, and the patient population was representative of the patient population receiving chemotherapy both in and outside of clinical trials.

The protocol specified included analyses of both the intent-to-treat (ITT) and the evaluable population, the evaluable population being classified as patients who received two courses of treatment and then had repeat scans. The ORRs for the ITT group were 32% and 25% for docetaxel and paclitaxel, respectively. Although the difference between the response rates in the ITT analysis did not reach significance, there was a significant difference ($P<0.05$) between the ORRs in the evaluable population, with the rates for docetaxel and paclitaxel being 37.0% and 25.9%, respectively. Median time to progression (TTP) in the ITT population was significantly increased from 3.6 months with paclitaxel to 5.7 months with docetaxel ($P<0.0001$), and the duration of response was also significantly greater in patients who received docetaxel compared with those who were given paclitaxel (7.5 versus 4.6 months; $P<0.05$). Docetaxel showed a superior overall survival (OS) of 15.4 months compared with 12.7 months for paclitaxel – a significant improvement of 2.7 months ($P=0.03$) (Fig. 1). Annual survival rates were also significantly increased for docetaxel compared with paclitaxel [10] with 50% more patients who received docetaxel alive at 2 years compared with those who received paclitaxel.

In this study, the incidence of Grade 3/4 neutropenia was significantly greater in patients who received docetaxel compared with those receiving paclitaxel (93.3% versus 54.5%; $P<0.0001$), as was the incidence of febrile neutropenia (15% and 2%, respectively; $P<0.001$). The incidences of anaemia and thrombocytopenia were similar

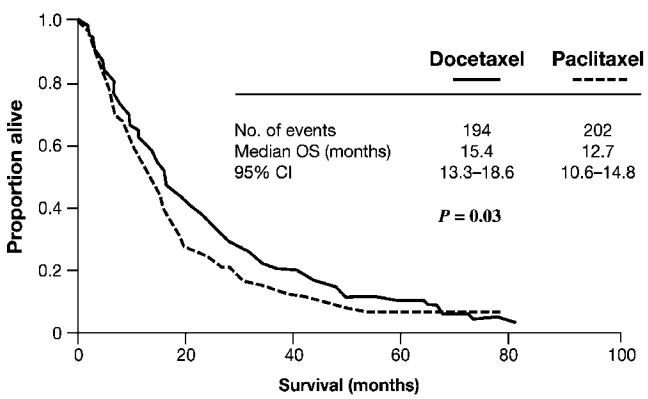

Fig. 1. TAX 311 overall survival (ITT analysis).

in both arms. There was also a significantly higher incidence of neuromotor toxicity and asthenia in patients in the docetaxel arm compared with those in the paclitaxel arm. However, on average, patients received approximately 50% more docetaxel than paclitaxel, as docetaxel was the more effective treatment [10]. Comparison of toxicity after four cycles of therapy revealed that the incidence of toxicities was similar between the two arms, with the incidence of Grade 3/4 haematological toxicity being approximately 35% in the docetaxel arm and 30% in the paclitaxel arm. Similarly, the incidence of Grade 3/4 non-haematological toxicities was approximately 20% in the docetaxel arm and 25% in the paclitaxel arm.

Patients received repeat scans after every cycle to assess the spread of the cancer to other sites. A significantly increased proportion of patients in the paclitaxel arm discontinued therapy due to disease progression; consequently, patients in the docetaxel group received a median number of six cycles of chemotherapy compared with four cycles for patients who received paclitaxel. Although dose reductions were performed, over 60% of patients received the full dose of docetaxel, even at cycle 12. Taking into consideration that the dose-limiting toxicity of docetaxel is neutropenia and prophylactic growth factor support was not permitted in this trial, this percentage indicates that many patients can be given the full docetaxel dose of 100 mg/m^2 without the need for dose reductions. The quality of life of patients in the TAX 311 trial was measured by the Functional Assessment of Cancer Therapy (FACT-B) measurement system, which is a global quality-of-life instrument that has been adapted for breast cancer patients. Analyses were performed comparing baseline measurements with those at cycle 4, as well as with those made at the end of the study. Despite the higher incidence of toxicities in the docetaxel arm compared with the paclitaxel arm, there was no difference in the quality of life experienced by patients receiving either treatment, at any point during the analyses.

A subsequent analysis examined the effects of crossover therapy in the TAX 311 trial. A large proportion of patients in both treatment arms – 70% of patients in the paclitaxel arm and 64% of patients in the docetaxel arm – received additional chemotherapy after progression on study treatment. Twenty-five percent of patients in the docetaxel arm received crossover therapy with paclitaxel, and the corresponding figure for patients in the paclitaxel arm who crossed over to receive docetaxel was 22%. The median survival after stopping study treatment did not differ significantly between the two arms and, as such, it was concluded that the survival advantage for docetaxel arose during initial trial therapy and not because of imbalances in the administration of, or in the effects of, post-trial therapy.

Since initiation of the TAX 311 trial, it has become obvious that the optimal dose and schedule for paclitaxel has not been established, and as such, the 3-weekly paclitaxel regimen used in the TAX 311 trial discussed above is now considered inferior to newer, weekly schedules. The TAX

311 trial was initiated in 1993 after the FDA requested a direct comparison of the approved dosing and schedules of each agent, which at this time, was 3-weekly. In addition, at the time of initiation of the TAX 311 study, there were no data for weekly paclitaxel schedules and in 2003, data from a direct comparison of weekly and 3-weekly paclitaxel regimens remained unavailable.

Several phase II studies have evaluated the safety and efficacy of weekly paclitaxel as single-agent therapy in patients with metastatic breast cancer reporting response rates of 22–53% in pretreated patients, with median TTPs in the range of 5–6 months [11–15]. A large, multicentre study by Perez and colleagues [16] investigated the activity and tolerability of weekly paclitaxel (80 mg/m^2) continuously until disease progression, in 212 women with previously treated metastatic breast cancer. The ORR was 21.5% (95% CI: 15.4–27.5%), and median TTP and OS duration were 142 days and 387 days, respectively. Seidman and colleagues [11] investigated weekly paclitaxel therapy at an initial dose of 100 mg/m^2 until disease progression, in 30 women who had received prior adjuvant and/or metastatic therapy, which achieved an ORR of 53%. Wist and colleagues [12] published the first report of first-line treatment with weekly paclitaxel (100 mg/m^2 as a 1-hour infusion) in 35 patients. The ORR was 40% and clinical benefit was observed in 67% of the patients. The TTP was 189 days, the duration of response was 180 days, and OS was 544 days. An Italian single-centre study [15] that evaluated weekly paclitaxel at a dose of 90 mg/m^2 in 58 patients without prior taxoid exposure reported a response rate of 44%.

Comparison of the relative efficacy of weekly and 3-weekly paclitaxel regimens is currently underway. The Cancer and Leukemia Group B (CALGB) 9840 study is a phase III study that will compare first-line therapy with a weekly paclitaxel regimen (100 mg/m^2, modified to 80 mg/m^2 after the initial weeks of therapy) with standard 3-weekly paclitaxel (175 mg/m^2) in 577 women [17]. An interim analysis demonstrated an ORR of 40% for patients in the weekly paclitaxel arm compared with 28% for those in the 3-weekly arm ($P = 0.017$). The median TTPs were 9 months and 5 months, respectively ($P = 0.0008$). However, these results are immature and the full analyses are awaited. As such, weekly paclitaxel remains unapproved, a situation that is unlikely to change owing to the expiration of the Taxol® patent in Europe and in the USA.

The first trial that has directly compared weekly paclitaxel and 3-weekly docetaxel regimens is the Eastern Co-operative Oncology Group (ECOG) 1199 study, and preliminary data from this study were released at the 2005 San Antonio Breast Cancer Symposium. Although this study concerns the use of these agents in the adjuvant setting, all patients had prior anthracycline exposure; therefore the effect of taxoid therapy in this study is analogous to the situation in the TAX 311 study. In the ECOG E1199 trial, 5052 patients with operable Stage II or IIIA, axillary node-positive or high-risk node-negative breast cancer were randomised to receive sequential therapy of either four cycles of 3-weekly paclitaxel (175 mg/m^2; control arm), 12 cycles of weekly paclitaxel (80 mg/m^2), four cycles of 3-weekly docetaxel (100 mg/m^2), or 12 cycles of weekly docetaxel (35 mg/m^2) following four 3-weekly cycles of AC (doxorubicin 60/cyclophosphamide 600 mg/m^2). This study, designed for a two-by-two comparison, revealed that there were no significant differences between the taxoids (HR = 0.985; $P = 0.83$), or between the schedules (HR = 1.04; $P = 0.54$) [18]. Whereas 3-weekly paclitaxel is now known to be a suboptimal schedule for administration of this agent, it is also known that a weekly regimen is an inappropriate schedule for administration of docetaxel, due to tolerability and quality-of-life issues. In addition, patients in the weekly paclitaxel arm received a 37% higher total dose than those in the 3-weekly paclitaxel arm. It could be argued that these factors have influenced the outcome of the primary objectives of this study. Furthermore, the results of this study were prematurely reported, with 200 fewer events than planned. With longer follow-up and adherence to the original statistical plan, it may be the case that future results bear more resemblance to those of the TAX 311 study.

1. Management of side effects

We have now had a decade to become accustomed to dealing with the side effects associated with the taxoids. The most serious side effect associated with docetaxel is the potential for development of febrile neutropenia in at-risk patients. However, there are two very effective strategies that can prevent its occurrence – dose reduction and prophylactic growth factor administration. The effectiveness of reducing the dose of docetaxel from 100 mg/m^2 to 75 mg/m^2 or 60 mg/m^2 was demonstrated in a soon to be published study by Mouridsen and colleagues [19]. The incidence of febrile neutropenia in patients receiving docetaxel was significantly reduced from 14% to 5%, with a reduction in dose from 100 mg/m^2 to 60 mg/m^2, as was docetaxel-related infection, being reduced from 7% to 2%. These dose reductions did not significantly reduce OS or TTP. Compared with a TTP of 13 weeks for the 100 mg/m^2 dose, the median TTP for the 75 mg/m^2 and 60 mg/m^2 doses were 15 weeks and 13 weeks, respectively, with a log-rank P-value for comparison of the three groups of 0.16. Similarly, OS for the 75 mg/m^2 and 60 mg/m^2 doses did not differ significantly from that achieved with the 100 mg/m^2 dose, with OS periods of 10 weeks, 11 weeks and 12 weeks, respectively (log-rank test for comparison of the three groups: $P = 0.35$). However, dose reduction from 100 mg/m^2 to 75 mg/m^2 or 60 mg/m^2 significantly reduced the ORR, the respective rates being 30%, 22% and 20%, with P-values of 0.026 for the between-group comparison and 0.037 for the pairwise comparison between 100 mg/m^2 and 60 mg/m^2 doses [19].

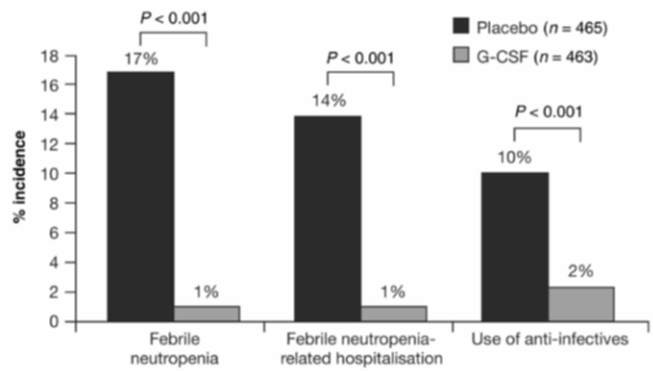

Fig. 2. The benefits of prophylactic granulocyte colony-stimulating factor.

A large, randomised study recently published by Vogel and colleagues [20] investigated the potential benefits of using prophylactic granulocyte colony-stimulating growth factor (G-CSF; 6 mg subcutaneously) on day 2 of each 3-week cycle of 100 mg/m^2 docetaxel. This trial reported a significant decrease in the incidence of febrile neutropenia (from 17% to 1%), the incidence of febrile neutropenia-related hospitalisation (from 14% to 1%), and the use of anti-infectives (from 10% to 2%), in patients who received prophylactic G-CSF compared with those who received placebo (Fig. 2).

These results provide very persuasive evidence of the striking benefits of G-CSF prophylaxis in patients with metastatic breast cancer who are receiving docetaxel. Various societies are currently in the process of drawing up treatment guidelines; for example, the National Comprehensive Cancer Network (NCCN) recommends prophylactic G-CSF support for regimens associated with a rate of febrile neutropenia of more than 20% [21].

With the recent addition of the taxoids to the armamentarium of breast cancer therapies and the subsequent publication of trial results, there are now many randomised trials that have demonstrated a survival benefit in patients with metastatic breast cancer. Docetaxel or docetaxel-containing regimens feature in a large proportion of these trials. In addition to the survival advantage exhibited by docetaxel over paclitaxel in the second-line setting, as reported in the TAX 311 trial [10], docetaxel has also shown a survival advantage over the combination of mitomycin plus vinblastine [22]. Combination therapy comprising docetaxel and doxorubicin has demonstrated a survival advantage over triple therapy comprising 5-fluorouracil, doxorubicin and cyclophosphamide (the FAC regimen) in the first-line setting [23], and combinations of docetaxel with capecitabine [24] or trastuzumab [25] have both demonstrated survival advantages over single-agent docetaxel in the second- and first-line settings, respectively. These results highlight the beneficial effects of using docetaxel either as monotherapy or as part of a combination therapy. Although both docetaxel and paclitaxel are fundamental components of therapy for metastatic breast cancer, the indirect comparison of trials, now backed by the results of the TAX 311 head-to-head study, demonstrates that docetaxel is the more clinically effective taxoid. The superior efficacy of docetaxel, compared with that of paclitaxel, which was achieved without impacting on patients' quality of life, supports the use of full-dose docetaxel in the adjuvant setting and, as such, docetaxel has become a cornerstone in the treatment of advanced and early-stage breast cancer. Improved definition of patient subgroups – including hormone receptor status based on, for example, HER2 status or, in the future, genetic subtyping – and the addition of novel agents to docetaxel-based regimens, will result in the individualisation of therapy and improved outcomes in the future.

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