Paclitaxel albumin (Abraxane®) as a substitute for docetaxel/paclitaxel for breast cancer therapy in the event of hypersensitivity reaction or contra-indication to steroids

January 2013

London Cancer New Drugs Group

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Summary

The evidence found to support the use of nab-paclitaxel (Abraxane®) indicates that Abraxane® is at least as effective as standard paclitaxel and docetaxel with a potentially beneficial safety profile in comparison. However, the evidence is only available for metastatic breast cancer and no evidence was found to support it’s use in the adjuvant or neoadjuvant setting.

Abraxane® is licensed as monotherapy for the treatment of metastatic breast cancer in patients who have failed first-line treatment for metastatic disease and for who standard, anthracycline containing therapy is not indicated. The licensed dose for this indication is 260mg/m² every 3 weeks. The substitution of paclitaxel/docetaxel for Abraxane® will, in the majority of cases, result in Abraxane® being used off-label. In addition, it is not clear what the weekly dose of Abraxane® would be although the optimal weekly dose in the phase II study was 150mg/m².

The request for CDF funding in this case is for breast cancer. However, taxane therapy is used for many different cancer indications and can cause hypersensitivity reactions for patients in other tumour groups.
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Background

The currently available taxanes, paclitaxel and docetaxel, play an important role in the treatment of breast cancer. Because the taxanes are highly hydrophobic, commercially available formulations include synthetic solvents to enable parenteral administration; paclitaxel contains a combination of polyethylated castor oil and ethanol as the vehicle, and polysorbate 80 and an ethanol diluent are the vehicles for docetaxel (1).

Although paclitaxel and docetaxel proved to have significant activity against breast cancer and other solid tumours, data indicates that the solvents polyethylated castor oil and polysorbate 80 directly contribute to the severe toxicities observed in patients treated with paclitaxel or docetaxel. Among the well-characterised, solvent-related toxicities are hypersensitivity reactions, which can rarely be fatal even with corticosteroid premedication, and prolonged, sometimes irreversible, peripheral neuropathy associated with demyelination and axonal degeneration (1).

nab-Paclitaxel (Abraxane®), an albumin-bound particle form of paclitaxel, was developed to avoid toxicities associated with the polyethylated castor oil vehicle in standard paclitaxel. Abraxane® is licensed as monotherapy for the treatment of metastatic breast cancer in patients who have failed first-line treatment for metastatic disease and for whom standard, anthracycline containing therapy is not indicated. The licensed dose for this indication is 260mg/m² every 3 weeks (4). Within the context of this review, the substitution of paclitaxel/docetaxel for Abraxane® will, in the majority of cases, result in Abraxane® being used off-label.

Epidemiology

The CDF clinician applicant estimated that 5% of breast cancer patients treated with taxanes would be suitable for Abraxane®. In advanced disease, it is estimated that 40% of patients are given taxanes, which would equate to 0.42/100,000 population. In early/locally advanced disease, it is estimated that 24% of patients are suitable for taxanes, which would equate to 1.5/100,000 population.

In total for both advanced and early/locally advanced, the number of patients eligible for Abraxane® would be 1.92/100,000.

Published data

Abraxane® as a substitute for solvent based paclitaxel

Abraxane® was compared with solvent based paclitaxel in an open-label, phase III study (1). Patients were randomly assigned (1:1) to receive treatment every three weeks with either Abraxane® (260mg/m² intravenously over 30 minutes without corticosteroid or antihistamine premedication or special infusion giving sets) or standard paclitaxel (175mg/m² intravenously over 3 hours with premedication and special giving sets).

Inclusion criteria included:

- Women who were at least 18 years of age.
- Histologically or cytologically confirmed, measurable metastatic breast cancer with an expected survival of at least 12 weeks.
- Had not received paclitaxel or docetaxel for metastatic carcinoma.
- Had not relapsed with metastatic disease within one year of adjuvant docetaxel or paclitaxel treatment.
- Had no other malignancy within the previous 5 years except non-melanoma skin cancer, cervical intraepithelial neoplasia, or in situ cervical cancer.

Exclusion criteria included:

- Clinical evidence of active brain metastases or a clinically serious concurrent illness.
- An ECOG performance status of more than 2.
- Received hormone therapy for 2 weeks or chemotherapy, immunotherapy, or another investigational drug for 4 weeks before administration of the first study dose.
- Pre-existing peripheral neuropathy of grade 1.
- A history of allergic or hypersensitivity reactions to the study drug or any of its excipients.

The primary efficacy measure was overall response rate (ORR). Secondary efficacy endpoints included time to progression (TTP) and overall survival. Quality-of-life (QOL) assessment data (ECOG performance status, scores from the European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30, and body weight) were collected.

The study was designed as a non-inferiority study, trying to prove that Abraxane® was at least 75% as active as standard paclitaxel, assuming an ORR 20% greater than the ORR of standard paclitaxel. Following enrolment, 229 patients received Abraxane® and 225 patients received standard paclitaxel.
Paclitaxel albumin (Abraxane®) as a substitute for docetaxel/paclitaxel for breast cancer

The mean age was 53.1 years in the Abraxane® arm (range 26–79 years) and 53.3 years in the standard paclitaxel arm (range 30–83 years). Baseline characteristics were well balanced between the two treatment arms. Approximately 60% had an ECOG performance status of 1 and 35% had a performance status of 0. Efficacy analyses were based on the intent-to-treat population.

The ORR was reported to be significantly greater for Abraxane® than for standard paclitaxel (33% vs. 19%, respectively; P=0.001). Median TTP was significantly longer with Abraxane® than with standard paclitaxel for all patients (23 vs. 16.9 weeks, respectively; hazard ratio [HR] =0.75; P=0.006). At the time of the analysis, the median censoring time for overall patient survival was 103 weeks for the Abraxane® arm and 101 for the standard paclitaxel arm. There was a trend towards greater median survival for patients treated with Abraxane® than with standard paclitaxel (65 vs. 55.7 weeks, respectively; P=0.374).

**Abraxane® as a substitute for docetaxel**

An open-label, randomised phase II study evaluated the safety and efficacy of three Abraxane® dosing regimens (weekly vs. three-weekly) and compared these dosing regimens to docetaxel administered at 100mg/m² every three weeks (2). A final analysis of these dosing regimens to docetaxel was published with mature results for overall survival (3).

Patients age ≥ 18 years with stage IV pathologically confirmed breast cancer, measurable disease, ECOG performance status of 0 to 2, and no prior chemotherapy for metastatic breast cancer were eligible for inclusion. If sensory neuropathy was present, it must have been ≤ grade 1. Prior neoadjuvant or adjuvant chemotherapy was allowed if at least 1 year had elapsed since therapy. Patients were excluded if they were receiving concurrent immunotherapy or hormonal therapy for breast cancer or had parenchymal brain metastases (unless stable), a history of class II to IV congestive heart failure, or other malignancy within the last 5 years that could affect the diagnosis or assessment of breast cancer. Patients receiving docetaxel were given oral corticosteroid premedication starting the day before docetaxel injection and infusion over 1 hour (n=74). Baseline characteristics were balanced across the four treatment groups. The mean age of patients was 54 years, and 83% were younger than 65 years. The majority of patients had visceral metastases and an ECOG performance status ≤ 1. Forty-three percent of patients had received prior chemotherapy in the adjuvant or neoadjuvant setting, and 10% of patients had grade 1 neuropathy before receiving study therapy.

The primary efficacy endpoint was overall response rate (ORR), defined as the percentage of patients achieving a complete response (CR) plus partial response (PR). Secondary efficacy endpoints included disease control rate (DCR; stable disease for ≥16 weeks or confirmed overall PR or CR), PFS, duration of response, and patient survival.

On the basis of independent radiologist review, both 150mg/m² (49%) and 100mg/m² (45%) weekly Abraxane® demonstrated a higher ORR than docetaxel (35%), but this did not reach statistical significance. The trend toward increased ORR was supported by investigator assessment with 150mg/m² (74%, P<0.001) and 100mg/m² (63%, P=0.002) weekly Abraxane® versus docetaxel (39%) reaching statistical significance. Comparisons of Abraxane® 300mg/m² every 3 weeks and docetaxel showed no statistical difference for ORR.

On the basis of both the independent radiologist and investigator review, DCR was significantly higher for patients receiving weekly Abraxane® compared with docetaxel. The independent radiologist-assessed DCRs for both the 150mg/m² (80%, P=0.017) and 100mg/m² (75%, P=0.009) Abraxane® weekly arms were statistically significant compared with docetaxel (58%). Although not statistically significant, independent radiologist-assessed DCR for Abraxane® 300mg/m² every 3 weeks (68%) was higher than docetaxel (58%). Abraxane® 150mg/m² weekly demonstrated a statistically longer PFS compared with docetaxel in both the independent radiologist (median 12.9 vs. 7.5 months, respectively; P=0.0065; HR=0.495) and investigator (median 14.6 vs. 7.8 months, respectively; P=0.012; HR=0.568) assessments. As evaluated by the independent reviewers, Abraxane® 100mg/m² weekly also prolonged PFS (>5 months) compared with docetaxel, but this result was not confirmed by the investigator assessment. In the Abraxane® 300mg/m² 3-weekly regimen, median PFS was longer compared with docetaxel for both the independent radiologist (median 11 vs. 7.5 months) and investigator (median 10.9 vs. 7.8) assessments, but these results did not reach statistical significance. Patient survival data were not mature at the time of data cut-off for this analysis.
Updated analysis of overall survival

An updated final analysis was reported for the phase II study comparing three Abraxane® dosing regimens with docetaxel (described above). The authors reported that the median overall survival was 33.8 months (95% CI 29.1–41.3 months) with Abraxane® 150mg/m² weekly compared with 22.2, 27.7, and 26.6 months in patients receiving Abraxane® 100mg/m² weekly, Abraxane® 300mg/m² every 3 weeks, and docetaxel, respectively (overall P = 0.047).

Safety

Abraxane® as a substitute for solvent based paclitaxel

Adverse event-related discontinuations, dose reductions, and dose delays were infrequent (3% to 7%) in both treatment arms, with no statistically significant differences noted between the groups. Consistent with the safety data, no differences in QOL were noted between the two treatment arms.

The incidence of hypersensitivity reactions (any grade) was low for both arms (<1% for Abraxane® and 2% for standard paclitaxel). No grade 3 or 4 treatment-related hypersensitivity reactions occurred in any of the patients in the Abraxane® arm despite the absence of premedication. Grade 3 hypersensitivity reactions occurred in the standard paclitaxel arm despite standard premedication (chest pain, two patients; allergic reaction, three patients).

The incidence of treatment-related grade 4 neutropenia was significantly lower in the Abraxane® arm than in the standard paclitaxel arm (9% vs. 22%, respectively; P<0.001). Febrile neutropenia was uncommon (<2%) in both study arms. Eight patients (3%) in the Abraxane® arm and 14 patients (6%) in the standard paclitaxel arm received growth factor treatment for neutropenia or leukopenia during the study.

Treatment-related grade 3 sensory neuropathy occurred more frequently in the Abraxane® arm than in the standard paclitaxel arm (10% vs. 2%). However, the dose of paclitaxel was higher in the Abraxane® arm.

Six patients in the Abraxane® arm (3%) and eight patients in the standard paclitaxel arm (4%) died during the study, all as a result of disease progression.

Abraxane® as a substitute for docetaxel

The updated analysis included updated safety results from the phase II study. Grade 4 neutropenia (75% vs. 5–9%), febrile neutropenia (8% vs. 1%), and grade 3 fatigue (19% vs. 0%–5%) occurred more frequently in the docetaxel arm compared with the Abraxane® arms. No cases of grade 4 sensory neuropathy were reported in any treatment arm.

Grade 3 sensory neuropathy was most frequent in the 150mg/m² weekly Abraxane® arm. Neutropenia and sensory neuropathy were the most common toxicities leading to dose reduction in the Abraxane® arms whereas neutropenia and febrile neutropenia were the most common toxicities leading to dose reduction in the docetaxel arm. Episodes associated with Abraxane® improved with interruption of treatment to grade 2 or 1 in a median 22 days and were easily managed with treatment interruption and dose reduction.

Cost

It is not clear exactly what the appropriate dose for weekly Abraxane® treatment would be, but the phase II study suggested that 150mg/m² weekly for 3 in 4 weeks would be suitable. The drug acquisition costs below have been described for both a weekly Abraxane® regimen and for a three-weekly Abraxane® regimen. It has been assumed that the weekly regimen would be given to patients with advanced breast cancer and the 3-weekly regimen would be given to patients with early breast cancer. The clinician has stated that the number of cycles would be 6 for advanced breast cancer and 3 for early breast cancer.

Early breast cancer

The proposed dose would be 260mg/m² every 3 weeks for 3 cycles. The cost for a 100mg vial of Abraxane® is £295 (including VAT). Using an average body-surface-area of 1.75m², the dose would be 455mg every 3 weeks which equates to 5 vials. The cost per dose (and per cycle) would therefore be £1475. If patients are treated for 3 cycles, the cost per patient for three cycles is £4425.

Assuming epidemiology of 1.5/100,000 (figure provided for early breast cancer), the cost for 3 cycles per 100,000 population would be £6638.

Advanced breast cancer

The proposed dose would be 150mg/m² weekly for three weeks, followed by 1 week break (4-week cycle), for 6 cycles. Using an average body-surface-area of 1.75m², the dose would be 263mg weekly for three weeks followed by one week break (4-week cycle) which equates to 3 vials. The cost per dose would be £885 per patient. The cost per cycle would be £2655 per patient. The cost for 6 cycles would be £15,930 per patient.

Assuming epidemiology of 0.42/100,000 (figure provided for advanced breast cancer), the cost for 6 cycles per 100,000 population would be £6690.
In total the estimated cost of substituting paclitaxel/docetaxel for Abraxane® in breast cancer patients experiencing hypersensitivity reactions or who have a contra-indication to steroids would be £13,328 (both early and advanced breast cancer patients).

**Service implications**

Patients experiencing hypersensitivity reactions to taxanes or who have contra-indications to steroids can receive a number of alternative treatments and so it is difficult to compare the service implications with Abraxane® to the alternative treatment(s) that patients receive. However, Abraxane® is administered intravenously and so requires an outpatient day unit appointment. Administration of Abraxane® can be over 30 minutes, in comparison to 3 hours for standard paclitaxel and 1 hour for docetaxel.

### Summary

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<table>
<thead>
<tr>
<th>Drug</th>
<th>Indication</th>
<th>Incidence (number of patients per 100,000 eligible for this treatment)</th>
<th>Average duration of treatment (taken from trial data)</th>
<th>Cost per month/cycle</th>
<th>Cost per 100,000 population per month/cycle</th>
<th>Cost per 100,000 for average treatment duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abraxane®</td>
<td>As a substitute for docetaxel/paclitaxel for breast cancer therapy in the event of hypersensitivity reaction or contra-indications to steroids</td>
<td>Early breast cancer: 1.5/100,000 Advanced breast cancer: 0.42/100,000</td>
<td>No average from trials but standard treatment is 3 cycles for early breast cancer and 6 cycles for advanced breast cancer</td>
<td>Early breast cancer: £1475 per cycle  Advanced breast cancer: £2655 per cycle</td>
<td>Early breast cancer: £2212 per cycle  Advanced breast cancer: £1115 per cycle</td>
<td>Early breast cancer: £6638  Advanced breast cancer: £6690</td>
</tr>
</tbody>
</table>
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References


Details of search strategy:

1. EMBASE; PACLITAXEL/; 56002 results.
2. EMBASE; BREAST CANCER/; 180511 results.
3. EMBASE; ALBUMIN/; 54214 results.
4. EMBASE; 1 AND 2 AND 3; 173 results.
5. EMBASE; 4 [Limit to: Human and English Language]; 140 results.
6. MEDLINE; PACLITAXEL/; 17532 results.
7. MEDLINE; BREAST NEOPLASMS/; 197799 results.
8. MEDLINE; ALBUMINS/; 15127 results.
9. MEDLINE; 6 AND 7 AND 8; 57 results.
10. EMBASE,MEDLINE; Duplicate filtered: [4 [Limit to: Human and English Language]], [6 AND 7 AND 8]; 197 results.

The document reflects the views of LCNDG and may not reflect those of the reviewers

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