Bevacizumab Combined with Two-weekly Paclitaxel as First-line Therapy for Metastatic Breast Cancer

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Abstract. Background: Metastatic breast cancer remains a major clinical issue despite progress achieved in recent years. Three randomised trials have demonstrated the benefit of combining bevacizumab with various taxane schedules. Herein, this study sought to investigate an alternative bevacizumab-taxane regimen as first-line treatment for metastatic breast cancer. Patients and Methods: Patients with metastatic breast cancer and who received first-line bevacizumab 10 mg/kg with paclitaxel 135 mg/m² every 2 weeks were studied. Results: All 43 enrolled patients were evaluable for efficacy and safety. The response rate was 58%; a further 40% achieved stable disease. After a median follow-up of 16 months, disease had progressed in 9 patients (21%). Treatment was well tolerated: grade 4 toxicities were absent; grade 3 adverse events comprised neutropenia (5%; no febrile neutropenia), hypertension (2%) and neuropathy (2%). Conclusion: This regimen may provide improved patient acceptability, quality of life and pharmacoeconomic benefits over a weekly paclitaxel schedule, and deserves further evaluation.

The crucial role of angiogenesis in tumour growth is firmly established and angiogenic pathways are important targets in treating many solid tumours, including breast cancer (BC). In metastatic BC, the only available anti-angiogenic agent is bevacizumab, which directly inhibits all isoforms of vascular endothelial growth factor. Three randomised, phase III trials (E2100, AVADO, RIBBON-1) in the first-line setting have demonstrated the efficacy and tolerability of combining bevacizumab with taxane-based therapy, showing significantly improved progression-free survival (PFS, the primary endpoint) and response rate compared with chemotherapy alone (1-3). Furthermore, the RIBBON-1 trial showed that the effect of combining bevacizumab with taxanes appears to apply more generally to standard first-line chemotherapy regimens, including anthracycline-based combinations and capcitabine.

While these trials provide evidence of the efficacy and tolerability of combining bevacizumab with weekly paclitaxel, 3-weekly docetaxel and 3-weekly nab-paclitaxel, this study aimed to determine the effect of combining bevacizumab with a 2-weekly schedule of paclitaxel. Similar dose-dense regimens have been evaluated in metastatic BC in combination with chemotherapy agents (4-8). A 2-weekly regimen is often used in the host clinic with the aim of improving patient convenience compared with weekly paclitaxel, while maintaining dose intensity. Previously published data demonstrated the efficacy of bevacizumab combined with 2-weekly paclitaxel in pretreated metastatic BC (9). Herein, the efficacy of this regimen in the first-line setting was assessed, including a bevacizumab maintenance phase to evaluate continuation of bevacizumab after completion of a fixed duration of chemotherapy.

Patients and Methods

Eligible patients had metastatic BC and had received no prior chemotherapy for advanced disease (adjuvant chemotherapy permitted). Patients with age 18-80, Eastern Cooperative Oncology Group (ECOG) performance status (PS) 0-1, life expectancy >12 months and adequate bone marrow reserve (WBC count ≥3,500/μl, neutrophils ≥2,000/μl, haemoglobin ≥10g/l, platelet count ≥100,000/μl), adequate liver and renal function (serum bilirubin ≤1.5 mg/dl, AST and ALT <than three times the upper limit of normal and serum creatinine ≤2 mg/dl ) and HER2-negative disease (or ineligible for trastuzumab) were eligible. According to national guidelines, the study was approved by the hospital scientific committee.

Patients received bevacizumab 10 mg/kg with paclitaxel 135 mg/m² (IV), on day 1 every 2 weeks for 6 months, with appropriate premedication and supportive care. Patients then received bevacizumab 15 mg/kg every 3 weeks as maintenance therapy until disease progression.
Study assessment. Response was assessed using Response Evaluation Criteria in Solid Tumors (RECIST) and patients were followed up every 3 months (10). Adverse events were graded according to World Health Organization criteria (11). Before entry, all patients underwent the following evaluations: medical history, physical examination, tumour evaluation - measurement and staging, ECOG performance status, electrocardiogram (ECG), complete blood cell count, serum chemistries, liver and renal function tests, serum tumour markers (CEA, CA15.3). Complete blood cell count, serum electrolytes and liver and renal function tests were measured before each treatment administration and 7-10 days after treatment.

Results

Patients. Between July 2007 and January 2009, 43 patients were enrolled (Table I). All were evaluable for efficacy and safety. None of the patients had cardiovascular comorbidities at baseline.

Efficacy and safety. The overall response rate was 58%, including complete responses in two patients (5%). Disease was stabilised in a further 17 patients (40%), giving a disease control rate of 98%. Only one patient had disease progression as best response. After median follow-up of 16 months, disease had progressed in 9 patients (21%) and therefore PFS and overall survival (OS) data are immature. Among these 9 patients, duration of PFS ranged from 1 to 16 months.

Toxicity was assessed using the standard WHO criteria. The regimen was very well tolerated: there was no toxicity grade ≥4 and the only grade 3 adverse events were neutropenia (5%), hypertension (2%) and neuropathy (2%) (Table II). There was no febrile neutropenia, arterial thromboembolism or proteinuria. All patients achieving a response or stable disease received maintenance bevacizumab. All treatment discontinuations were due to disease progression.

Discussion

This single-centre study suggests that bevacizumab combined with 2-weekly paclitaxel is feasible, active and well tolerated. There were no grade 4 toxicities and grade 3 toxicities were rare. The lack of proteinuria, typically associated with anti-angiogenic therapy, is perhaps surprising.

In the E2100 trial of bevacizumab with weekly paclitaxel, grade ≥3 adverse events included hypertension (16% of patients), proteinuria (3%), arterial thromboembolic events (3.6%), venous thromboembolic events (3.0%), bleeding (2.2%), congestive heart failure (2.2%), and gastrointestinal perforation (0.6%) (12). The placebo-controlled AVADO trial enabled a more robust assessment of the impact of bevacizumab on chemotherapy and demonstrated a 3.4% incidence of grade ≥3 hypertension with bevacizumab 15 mg/kg every 3 weeks and a 0.4% incidence of grade ≥3 proteinuria (2). The safety profile of bevacizumab in a broader population more representative of routine oncology practice has been well characterised in the ATHENA study, which evaluated first-line bevacizumab with taxane-based therapy in more than 2000 patients with locally recurrent or metastatic BC (13). A large proportion of patients (n=756; 37%) received bevacizumab in combination with single-agent paclitaxel, given using a 3-weekly (n=285), weekly (n=310) or alternative schedule (n=161) (14). Among patients receiving bevacizumab combined with single-agent paclitaxel, grade ≥3 hypertension was reported in 3.3%, grade ≥3 proteinuria in 1.5%, and pulmonary embolism in 0.9%. The incidence of grade 3 hypertension in our study

### Table I. Baseline patient characteristics (n=43).

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age, years (range)</td>
<td>56 (38-78)</td>
</tr>
<tr>
<td>≤40, n (%)</td>
<td>3 (7%)</td>
</tr>
<tr>
<td>40-49, n (%)</td>
<td>5 (12%)</td>
</tr>
<tr>
<td>50-59, n (%)</td>
<td>20 (47%)</td>
</tr>
<tr>
<td>60-69, n (%)</td>
<td>9 (21%)</td>
</tr>
<tr>
<td>≥70, n (%)</td>
<td>6 (14%)</td>
</tr>
</tbody>
</table>

### Table II. Toxicity according WHO criteria (n=43).

<table>
<thead>
<tr>
<th>Grade</th>
<th>All grades</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia</td>
<td>16 (37%)</td>
<td>4 (9%)</td>
<td>10 (23%)</td>
<td>2 (5%)</td>
<td>0</td>
</tr>
<tr>
<td>Anaemia</td>
<td>2 (5%)</td>
<td>2 (5%)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Hypertension</td>
<td>7 (16%)</td>
<td>1 (2%)</td>
<td>5 (12%)</td>
<td>1 (2%)</td>
<td>0</td>
</tr>
<tr>
<td>Neuropathy</td>
<td>9 (21%)</td>
<td>3 (7%)</td>
<td>5 (12%)</td>
<td>1 (2%)</td>
<td>0</td>
</tr>
</tbody>
</table>

*Assessed by serum concentration of HER2 extracellular domain; these patients did not receive trastuzumab as their disease was not HER2-positive by standard criteria.*

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(2.3%) is consistent with these findings and the absence of proteinuria may simply reflect the very small sample size.

The 58% response rate is within the range reported in randomised, phase III trials of bevacizumab–taxane therapy (50%-64%), although cross-trial comparison has obvious limitations, especially because the current study population comprised a high percentage of patients with locally advanced BC. The 98% disease control rate in the current study is noteworthy. Only one patient showed primary resistance to bevacizumab-containing therapy. This is consistent with findings from AVADO, in which only 4% of patients receiving bevacizumab 15 mg/kg in combination with docetaxel had progressive disease as their best response (2).

A 2-weekly paclitaxel regimen is not used routinely in clinical practice in many countries. However, convenience and resource savings are likely when paclitaxel is administered every 2 weeks compared with weekly administration. A limitation of the current study is the lack of quality of life and pharmacoeconomic evaluation, but the Authors consider that the benefits of 2-weekly over weekly paclitaxel administration are self evident.

This 2-weekly bevacizumab–paclitaxel regimen shows promising activity with an acceptable safety profile in advanced BC. The observed activity supports further evaluation in a larger patient population to determine whether it provides a valid alternative to more conventional regimens. If efficacy is similar to weekly paclitaxel with bevacizumab, this regimen might represent an attractive schedule, potentially offering quality of life benefits and resource savings.

References


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