New agents in breast cancer — minisymposium

Current status of Taxotere® (docetaxel) as a new treatment in breast cancer

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Summary

Therapy for advanced breast cancer has not improved significantly in recent years, remaining strictly palliative in nature and intent. One approach to increase the effectiveness of the treatment is the introduction of active new drugs. Taxotere® (docetaxel) is a taxoid derivative isolated from the needles of the European yew, Taxus baccata. Taxotere promotes the assembly of microtubules and inhibits their depolymerization. One EORTC Clinical Screening Group (CSG) phase II trial using Taxotere at 100 mg/m², 1 hour infusion without routine premedication for hypersensitivity reactions, in first line chemotherapy, indicates a high anti-tumor activity: 5 complete and 18 partial responses in 32 patients assessable for response (overall response rate 72%, 95% CI 53%-86%). Other studies confirm this activity in first line and second line chemotherapy for advanced disease and in patients who are refractory to anthracycline containing regimens. Grades III and IV neutropenia without major infection, and grades I and II skin toxicity, were frequently observed adverse events. A fluid retention syndrome (chronic cumulative and non life-threatening toxicity) has been noted in patients treated with Taxotere. Methods for controlling fluid retention — dose reduction to 75 mg/m² (which has little effect) or routine premedication from the start of treatment — are currently being studied.

Introduction

Breast cancer is the most common malignancy affecting women in the Western World. In Europe, the yearly incidence is approximately 80 cases per 100,000 women, and approximately half of these will die of the disease. Adjuvant therapy delays systemic recurrence and improves survival for a small fraction of these patients [1]. Therapy for advanced disease remains strictly palliative in nature and intent and has not significantly improved the final outcome in recent years [2]. Thus, advanced breast cancer, whether primary or metastatic, remains an incurable disease. In spite of clinical response to standard hormonal, chemotherapeutic, or combination hormonal/chemotherapeutic regimens, the median survival of women with metastatic disease is approximately 2 years [3].

One therapeutic approach to try to improve the
results is to use dose-intensive regimens combining currently available drugs with either recombinant growth factors or autologous bone marrow or peripheral blood stem cell support. Although an improvement in response rate [4] can be demonstrated, no definite survival advantage has yet been achieved in phase III trials.

Another alternative approach to increase the effectiveness of treatment is the introduction of active new drugs. A recent review [5] of single agent efficacy of cytotoxic compounds indicates that anthracyclines, alkylating agents, antimetabolites, and vinca alkaloids are among the most active drugs in the treatment of advanced breast cancer. However, a wide variation of results is found when the data are analyzed according to the presence or absence of prior chemotherapy for advanced disease. For patients who have already received chemotherapy for the treatment of metastatic disease, the response rates in clinical trials range from 4 to 32%. This group of patients is less likely to respond due to deterioration of performance status, high tumor burden, decrease of marrow reserves, and possible acquired drug resistance. In previously untreated patients, response rates range from 20 to 73%, but complete responses are rare (less than 20%).

The taxoids Taxol and Taxotere represent a novel class of antineoplastic drugs sharing a similar mechanism of action: they promote microtubule assembly and inhibit depolymerization of microtubules, which results in killing cancer cells in vitro as well as in vivo [6,7].

The clinical development of Taxol was initially hampered by hypersensitivity reactions, though the use of routine premedication and longer infusion has somewhat decreased these reactions. There has therefore been considerable interest in related agents which might cause less hypersensitivity.

Taxotere is a new cytotoxic agent hemi-synthesized from an extract of the needles of the European yew, *Taxus baccata*, which was found to be very active in preclinical studies. In these studies, Taxotere was 2.5 fold more potent than Taxol as an inhibitor of cell replication and 5 fold more potent than Taxol against Taxol resistant cells [7]. *In vivo*, Taxotere was active in both murine and human xenografted tumors. In a comparative trial, Taxotere was 2-6 fold more active than Taxol on B16 melanoma [6].

Five phase I trials with Taxotere have been conducted, using various schedules and durations of administration [8-12]. No routine premedication for hypersensitivity reactions was used. The details and pertinent findings of these studies are presented in Table 1.

Neutropenia is the dose limiting toxicity. The major difference in toxic reactions among the Taxotere schedules is the appearance of oral mucositis in the 24 h, 6 h, and daily x 5 regimens leading to episodes of febrile neutropenia. Worth

<table>
<thead>
<tr>
<th>Schedulea</th>
<th>Maximum tolerated dose</th>
<th>Dose limiting toxicity</th>
<th>Other significant toxicities</th>
<th>Phase II recommended dosea</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-2 h infusion</td>
<td>115 mg/m²</td>
<td>Neutropenia</td>
<td>Skin</td>
<td>100 mg/m²</td>
<td>[8]</td>
</tr>
<tr>
<td>24 h infusion</td>
<td>90 mg/m²</td>
<td>Neutropenia</td>
<td>Mucositis</td>
<td>70 mg/m²</td>
<td>[9]</td>
</tr>
<tr>
<td>1 h x 5 days</td>
<td>80 mg/m² (16 mg/m² x 5)</td>
<td>Neutropenia</td>
<td>Mucositis</td>
<td>70 mg/m² (14 mg/m² x 5)</td>
<td>[10]</td>
</tr>
<tr>
<td>6 h infusion</td>
<td>100 mg/m²</td>
<td>Neutropenia</td>
<td>Mucositis</td>
<td>80 mg/m²</td>
<td>[11]</td>
</tr>
<tr>
<td>1 h on days 1-8</td>
<td>55 mg/m² d1 + d8</td>
<td>Neutropenia</td>
<td>Asthenia</td>
<td>100 mg/m² (50 mg/m² d1 + d8)</td>
<td>[12]</td>
</tr>
</tbody>
</table>

a every 3 weeks

Reference: [4-7, 8-12]