Capecitabine and vinorelbine in elderly patients (≥65 years) with metastatic breast cancer: a phase I trial (SAKK 25/99)

On behalf of the Swiss Group of Clinical Cancer Research (SAKK)

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Background: Few chemotherapy regimens are suitable for the treatment of elderly patients with advanced breast cancer. With the aim of finding a regimen with a low burden of subjective non-overlapping toxic effects, vinorelbine and capecitabine were chosen to be investigated in a phase I dose-finding study.

Patients and methods: Thirty-six patients with advanced breast cancer were stratified for the presence of bone and non-bone involvement and treated at four dose levels from capecitabine 800 mg/m² orally days 1–14 and vinorelbine 20 mg/m² intravenously days 1 and 8, to capecitabine 1250 mg/m² orally days 1–14 and vinorelbine 25 mg/m² intravenously days 1 and 8, for a maximum of six cycles. None of the patients had received prior chemotherapy for metastatic/advanced disease. Fifty-three per cent of patients with bone metastases and 67% of patients without bone metastases had visceral disease. The median age was 70 years for the 15 with bone involvement patients and 73 years for the 21 without bone involvement patients.

Results: Twenty-eight patients were fully evaluable for hematological dose-limiting toxicity (DLT), and all patients for other DLTs and for antitumor activity. One DLT with grade 3 venous thrombosis at dose level 2 and two dose-limiting neutropenia events at level 3 occurred in patients without bone involvement. Two dose-limiting neutropenia events were observed at dose level 2 for patients with bone involvement. Thus, the recommended dose was defined at level 1 (capecitabine 1000 mg/m² days 1–14 and vinorelbine 20 mg/m² days 1 and 8) for patients with bone involvement. For patients without bone involvement, the recommended dose was at level 2 (capecitabine 1250 mg/m² days 1–14 and vinorelbine 20 mg/m² days 1 and 8). For patients without bone involvement the overall response rate was 48% and the time to progression (TTP) was 4.5 months [95% confidence interval (CI) 3.3–6.9]. For patients with bone involvement the overall response rate was 53% and TTP was 5.3 months (95% CI 2.7–7.8).

Conclusions: This regimen of capecitabine and vinorelbine is well tolerated and effective in elderly patients with metastatic breast cancer. Toxicity was mainly hematological and was observed at a lower dose in patients with bone involvement. A phase II study with the two different dose levels for elderly patients with and without bone involvement is currently being conducted.

Key words: capecitabine, elderly patients, metastatic breast cancer, vinorelbine

Introduction

Elderly women are more likely than younger patients to have breast cancer that will metastasize, as more of them are node-positive. Nevertheless, they are less likely to be offered chemotherapy and radiation treatment and are significantly underrepresented in prospective clinical trials [1].

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Curigliano et al. [2] presented data from 3000 postmenopausal women treated for invasive breast cancer in the adjuvant setting at the European Institute of Oncology. Patients were stratified for age: 50 to <65 years, 65 to <75 years and ≥75 years. While surgical approaches were similar in the three groups, only 6.4% of patients ≥75 years had been offered chemotherapy and only 34.7% received standard radiotherapy after lumpectomy. Younger postmenopausal patients were offered chemotherapy in 35.4% of cases and radiotherapy in ~60%, despite the fact that 62% of the older patients had node involvement compared with 52% of the younger ones. In estrogen receptor-positive disease, hormonal treatment was offered...
to almost 90% of patients ≥75 years old, as opposed to 77% in the younger groups. These data show clearly that elderly patients are at risk of not receiving appropriate treatment due to the prejudice that they will not tolerate it.

Only a few chemotherapy combinations have been designed for the specific needs of elderly patients, especially with regard to the toxicity profile. Therefore, the need to investigate better treatments for this age group seems to be even greater than for younger patients.

In the adjuvant setting, chemotherapy regimens including cyclophosphamide, methotrexate, 5-fluorouracil (5-FU) or doxorubicin appear to have similar or inferior efficacy in elderly patients, even though the cost in terms of toxicity is considerably higher [3]. This finding is in accordance with a widely accepted belief that dose intensity is much more difficult to achieve and maintain in elderly patients than in younger ones.

A possible solution might be the combination of capcitabine and vinorelbine, as there is little overlapping toxicity between these two drugs. Vinorelbine alone has been tested in several phase II studies in elderly patients (≥65 years) with metastatic breast cancer [4, 5] and advanced non-small-cell lung cancer [6, 7]. In pretreated patients with advanced breast cancer, grade 3/4 diarrhea and grade 3/4 hand–foot syndrome were observed in 10% to 14% of patients with capcitabine monotherapy at 2500 mg/m² per day for 2 weeks, followed by 1 week of rest [8]. In anthracycline-pretreated patients, capcitabine was compared with paclitaxel [9]. Twenty-two per cent of the patients on the capcitabine schedule showed grade 3/4 events, as opposed to 58% on the paclitaxel schedule. Compared with CMF (cyclophosphamide, methotrexate and 5-FU), capcitabine showed more grade 3/4 adverse events, especially due to hand–foot syndrome and diarrhea [10]. In combination with fully dosed taxanes, the safe dose for capcitabine seems to be 825 mg/m² per day for 14 days [11, 12].

**Patients and methods**

Patients ≥65 years with histologically or cytologically documented metastatic or locally advanced breast cancer without prior chemotherapy for metastatic disease were eligible. Two strata, for patients with and for patients without bone involvement, were run. Adjuvant chemotherapy had to be completed at least 6 months prior to trial entry. Prior hormonal treatment for advanced disease was permitted. Eligibility criteria included WHO performance status ≤2, normal peripheral blood count, aspartate aminotransferase and alanine aminotransferase ≤2× the upper normal limit (UNL), and creatinine ≤1.5× UNL. In March 2001 an amendment was added requesting that patients with a calculated creatinine clearance (Cockcroft–Gault formula) between 30 and 50 ml/min should receive 75% of the capcitabine dose. Bisphosphonates were allowed if at least one extraskeletal indicator lesion was present. All patients signed written informed consent forms. Exclusion criteria were known or suspected central nervous system metastases, pre-existent peripheral neuropathy grade ≥2, concomitant steroids and previous or present malignant disease other than adequately treated in situ carcinoma of the cervix or basal or squamous cell carcinoma of the skin. Patients with radiotherapy involving >30% of bone marrow or mucosa or administered to indicator lesions were not eligible.

Baseline evaluation included patient history, physical examination, complete blood cell count (CBC), biochemistry, electrocardiogram, bone scan and radiological imaging of indicator lesions (computed tomography scan, X-ray). During therapy, CBC was performed twice weekly (not more than 4 days apart) during the first cycle, and weekly thereafter, and biochemistry was performed before each cycle. Tumor response of measurable and evaluable sites of disease was repeated after every other cycle and at the end of study.

Treatment was given on an outpatient basis and planned to continue for a maximum of six cycles unless there was evidence of disease progression, unacceptable toxicity or patient refusal.

Vinorelbine (Navelbine™) was administered as bolus injection on days 1 and 8 preceded and followed by 250 ml NaCl 0.9% infusion to prevent venous irritation.

Cапcitabine (Xeloda™) was supplied by Roche and given orally twice daily, 30 min after a meal, on days 1–4 and 8, 2 cycles weekly. Control of treatment compliance was not planned for this trial. Cycles were repeated every 21 days. Prophylactic antiemetic treatment was given according to local rules.

If the absolute neutrophil count (ANC) on day 8 was between 0.9 and 1.5×10⁹/l, the vinorelbine dose was reduced by 50%. With an ANC <0.9×10⁹/l vinorelbine was omitted. If grade IV hematological toxicity occurred for ≥4 days, vinorelbine was reduced by 25% in the next cycle. An adequate hematological recovery on day 21 (ANC ≥1.0×10⁹/l and platelets ≥100×10⁹/l) was necessary to continue with the next cycle. For skin and mucosal toxicity, capcitabine was reduced according to protocol (Table 1). Dose escalation was carried out according to the scheme in Table 2, with doses being assigned at study entry, starting at dose level 0. No intra-patient dose escalation was allowed. The decision for dose escalation was based exclusively on the toxicity observed during the first cycle of chemotherapy. At each dose level, three patients were included. If none of them showed a dose-limiting toxicity (DLT), the combination in the next dose level was evaluated. If one patient showed DLT, three additional patients were included on the same dose level. If two or more patients out of six at the same dose level showed DLT, the dose escalation was to be stopped and the next lowest dose level was to be considered as the recommended dose. Toxicity was recorded according to the National Cancer Institute (NCI) Common Toxicity Criteria (CTC) v. 2.0.

**Table 1. Dose modification of capcitabine in cases of skin and mucosal toxicity, and diarrhea**

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Grade 2</th>
<th>Grade 3</th>
<th>Grade 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>First appearance of any toxicity</td>
<td>Interrupt treatment until resolved to grade 0–1; no dose reduction</td>
<td>Interrupt treatment until resolved to grade 0–1; continue with 75%</td>
<td>Discontinue treatment; if in the best interest of the patient continue with 50% once toxicity has resolved to grade 0–1</td>
</tr>
<tr>
<td>Second appearance of same toxicity</td>
<td>Interrupt treatment until resolved to grade 0–1; continue with 75%</td>
<td>Interrupt treatment until resolved to grade 0–1; continue with 50%</td>
<td>Discontinue treatment</td>
</tr>
<tr>
<td>Third appearance of same toxicity</td>
<td>Interrupt treatment until resolved to grade 0–1; continue with 75%</td>
<td>Interrupt treatment until resolved to grade 0–1; continue with 75%</td>
<td>Discontinue treatment</td>
</tr>
<tr>
<td>Fourth appearance of same toxicity</td>
<td>Discontinue treatment</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Cancer Institute of Canada Common Toxicity Criteria. Each cycle was considered fully evaluable for hematological toxicity only in cases with twice-weekly CBC assessments not more than 4 days apart.

DLT was defined as ANC <0.5 \times 10^9/l for four or more consecutive days, platelet count <25 \times 10^9/l for four or more consecutive days, any grade 3 or 4 non-hematological toxicity except alopecia, nausea and vomiting, dose reduction of vinorelbine on day 8, and treatment interruption due to chemotherapy-related toxicity grade \geq 2 and lasting \geq 1 week.

Response was defined according to WHO criteria. Osteolytic lesions documented by X-ray were considered evaluable, but not measurable, while sclerotic lesions and bone metastases documented only by bone scan were considered non-evaluable.

Time to progression (TTP) was calculated from the date of registration until tumor progression occurred. If a patient started any further antineoplastic treatment before progression had occurred, TTP was censored at the starting date of the new treatment.

Results

From April 1999 to March 2001 a total of 36 patients were treated with a combination of capecitabine and vinorelbine as first-line chemotherapy for metastatic or locally advanced breast cancer. Fifteen patients had bone involvement and 21 patients had no bone involvement.

Patient characteristics

For patients with bone involvement the median age was 70 years (range 65–85) and for patients without bone involvement was 73 years (range 66–83). Most patients had a WHO performance status of 0 or 1. Visceral disease was present in 61% of all patients (see Table 3 for details).

Treatment

In total, 69 cycles were administered to the 15 patients with bone involvement (mean 4.6 per patient) and 96 cycles to the 21 patients without bone involvement (mean 4.5 per patient).

Toxicity

Twenty-eight out of 36 patients were fully evaluable for hematological toxicity with twice weekly CBC in the first cycle, and all patients were evaluable for all other toxicities. Eight out of 36 patients did not have the required number of differential blood counts in cycle 1 to exclude a DLT as defined above, and had to be replaced. However, these patients are included in the efficacy analysis and in the analysis for all other toxicities.

In patients with bone involvement, no DLT occurred at dose levels 0 and 1, whereas at dose level 2, two DLTs were seen: one patient experienced grade 2 and one grade 3 neutropenia, leading to a dose reduction of vinorelbine on day 8. The dose escalation was thus stopped at dose level 2 and dose level 1 was declared the recommended dose.

For the patients without bone involvement, no DLT was seen at dose levels 0 and 1. At dose level 2, one DLT, a grade 3 thrombotic event, was observed and three additional patients were treated on the same dose level. No further DLT was seen in these three patients and therefore dose escalation to dose level 3 was performed.

At dose level 3, two hematological DLTs occurred: one patient had grade 2 neutropenia on day 8 leading to a dose reduction of vinorelbine, and the second patient had grade 4 neutropenia for more than four consecutive days. Thus, dose level 2 was defined as the recommended dose.

Hematological side-effects were the most common toxicity with this regimen and were responsible for all but one DLT.

Table 2. Dose levels

<table>
<thead>
<tr>
<th>Dose level</th>
<th>Capecitabine (mg/m²) days 1–14</th>
<th>Vinorelbine (mg/m²) days 1 and 8</th>
</tr>
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<tbody>
<tr>
<td>0</td>
<td>800</td>
<td>20</td>
</tr>
<tr>
<td>1</td>
<td>1000</td>
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</tr>
<tr>
<td>2</td>
<td>1250</td>
<td>20</td>
</tr>
<tr>
<td>3</td>
<td>1250</td>
<td>25</td>
</tr>
<tr>
<td>4</td>
<td>1500</td>
<td>25</td>
</tr>
<tr>
<td>5</td>
<td>1500</td>
<td>30</td>
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Table 3. Patient characteristics

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>With bone involvement (n = 15)</th>
<th>Without bone involvement (n = 21)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median</td>
<td>70</td>
<td>73</td>
</tr>
<tr>
<td>Range</td>
<td>65–85</td>
<td>66–83</td>
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<table>
<thead>
<tr>
<th>Weight (kg)</th>
<th>With bone involvement (n = 15)</th>
<th>Without bone involvement (n = 21)</th>
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<tbody>
<tr>
<td>Median</td>
<td>63</td>
<td>66</td>
</tr>
<tr>
<td>Range</td>
<td>45–85</td>
<td>42–97</td>
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<th>WHO performance status</th>
<th>With bone involvement (n = 15)</th>
<th>Without bone involvement (n = 21)</th>
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<tr>
<td>Bone</td>
<td>15</td>
<td>0</td>
</tr>
<tr>
<td>Liver</td>
<td>9</td>
<td>9</td>
</tr>
<tr>
<td>Lung</td>
<td>2</td>
<td>9</td>
</tr>
<tr>
<td>Lymph nodes</td>
<td>3</td>
<td>14</td>
</tr>
<tr>
<td>Skin</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Pleura</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Other</td>
<td>5</td>
<td>13</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Site of disease</th>
<th>With bone involvement (n = 15)</th>
<th>Without bone involvement (n = 21)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone</td>
<td>15</td>
<td>0</td>
</tr>
<tr>
<td>Liver</td>
<td>9</td>
<td>9</td>
</tr>
<tr>
<td>Lung</td>
<td>2</td>
<td>9</td>
</tr>
<tr>
<td>Lymph nodes</td>
<td>3</td>
<td>14</td>
</tr>
<tr>
<td>Skin</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Pleura</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Other</td>
<td>5</td>
<td>13</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Previous therapy</th>
<th>With bone involvement (n = 15)</th>
<th>Without bone involvement (n = 21)</th>
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</thead>
<tbody>
<tr>
<td>Adjuvant</td>
<td>8</td>
<td>9</td>
</tr>
<tr>
<td>Palliative</td>
<td>11</td>
<td>8</td>
</tr>
<tr>
<td>Previous radiotherapy</td>
<td>11</td>
<td>12</td>
</tr>
<tr>
<td>Adjuvant chemotherapy</td>
<td>8</td>
<td>9</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Neurological symptoms</th>
<th>With bone involvement (n = 15)</th>
<th>Without bone involvement (n = 21)</th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>13</td>
<td>19</td>
</tr>
<tr>
<td>Mild</td>
<td>2</td>
<td>2</td>
</tr>
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</table>
As expected, patients with bone involvement and patients ≥70 years old, irrespective of bone involvement, were more prone to hematological toxicity, and DLTs were already seen at dose level 2. Patients without bone involvement had a greater tolerance, and DLTs were seen at dose level 3. In 64 cycles given to 12 patients <70 years, two events of grade 3/4 neutropenia were observed, whereas in 101 cycles given to 24 patients ≥70 years, 13 events of grade 3/4 neutropenia occurred. This difference is significant (P = 0.023).

Other toxicities were mostly moderate (Table 6). Grade 1 nausea, diarrhea, alopecia, asthenia and paresthesia were the most frequent non-hematological toxicities. Grade 3/4 toxicities included one grade 3 thromboembolic event that was also listed as DLT, one grade 3 stomatitis and one grade 3 diarrhea. A dose reduction of capecitabine was necessary to prevent further mucosa toxicity in one patient. Grade 2 alopecia was seldom observed. Hand–foot syndrome did not occur, probably due to the rather low dose of capecitabine.

Serum creatinine was an inclusion criterium. We calculated the creatinine clearance according to the Cockroft–Gault formula for females using baseline body weight and serum creatinine of each cycle. Data from 175 cycles were available: in 77 cycles the creatinine clearance was <50 ml/min; in 75 cycles it was between 50 and 80 ml/min (mild renal impairment); and in 13 cycles it was >80 ml/min (normal renal function).

One grade 3 diarrhea and stomatitis was seen in the group with creatinine clearance between 50 and 80 ml/min. Nearly all other grade 3/4 toxicities were hematological side-effects, with a trend towards the patients with impaired renal function: 11 grade 3/4 toxicities out of 77 cycles with creatinine clearance <50 ml/min; 12 grade 3/4 toxicities out of 75 cycles with creatinine clearance between 50 and 80 ml/min; and two grade 3/4 toxicities out of 13 cycles with creatinine clearance >80 ml/min

### Efficacy

All patients were evaluable for response. Responses were seen at all dose levels. The response rate for patients with bone involvement was 53% and for patients without bone involvement was 48% (Table 7). An additional 13% and 38% of patients with and without bone involvement, respectively, achieved disease stabilization. The TTP for patients without bone metastases was 4.5 months [95% confidence interval (CI) 3.3–6.9] and for patients with bone metastases 5.3 months (95% CI 2.7–7.8). Seven out of 21 patients without bone involvement and four out of 15 patients with bone involvement received a further, mostly hormonal, antitumor treatment to maintain the effect of the chemotherapy before disease progression occurred, thus leading to a censored TTP.

### Table 4. Hematological toxicities by patient (all cycles)

<table>
<thead>
<tr>
<th></th>
<th>With bone involvement (n = 15)</th>
<th>Without bone involvement (n = 21)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia grade 3</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>Neutropenia grade 4</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Thrombopenia grade 3</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Thrombopenia grade 4</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Anemia grade 3</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Anemia grade 4</td>
<td>2</td>
<td>0</td>
</tr>
</tbody>
</table>

### Table 5. Frequency of hematological toxicities (all cycles)

<table>
<thead>
<tr>
<th></th>
<th>With bone involvement (% of 69 cycles)</th>
<th>Without bone involvement (% of 96 cycles)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia grade 3</td>
<td>10.1</td>
<td>3.1</td>
</tr>
<tr>
<td>Neutropenia grade 4</td>
<td>2.9</td>
<td>3.1</td>
</tr>
<tr>
<td>Thrombopenia grade 3</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Thrombopenia grade 4</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Anemia grade 3</td>
<td>1.4</td>
<td>0</td>
</tr>
<tr>
<td>Anemia grade 4</td>
<td>2.9</td>
<td>0</td>
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### Table 6. Frequency of non-hematological toxicities (per patient)

<table>
<thead>
<tr>
<th></th>
<th>Stratum with bone involvement (n = 15)</th>
<th>Stratum without bone involvement (n = 21)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nausea grade 1</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>Nausea grade 2</td>
<td>1</td>
<td>4</td>
</tr>
<tr>
<td>Stomatitis grade 1</td>
<td>1</td>
<td>3</td>
</tr>
<tr>
<td>Stomatitis grade 2</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Stomatitis grade 3</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Diarrhea grade 1</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Diarrhea grade 2</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Diarrhea grade 3</td>
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<td>1</td>
</tr>
<tr>
<td>Alopecia grade 1</td>
<td>1</td>
<td>5</td>
</tr>
<tr>
<td>Alopecia grade 2</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Neurosensory grade 1</td>
<td>4</td>
<td>6</td>
</tr>
<tr>
<td>Phlebitis grade 1</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Phlebitis grade 2</td>
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<td>1</td>
</tr>
<tr>
<td>Asthenia grade 1</td>
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</tr>
<tr>
<td>Asthenia grade 2</td>
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<td>5</td>
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### Table 7. Best overall response

<table>
<thead>
<tr>
<th></th>
<th>With bone involvement (n = 15)</th>
<th>Without bone involvement (n = 21)</th>
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<tbody>
<tr>
<td>Complete response</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Partial response</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>Stable disease</td>
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<td>8</td>
</tr>
<tr>
<td>Disease progression</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>Response rate [% (95% CI)]</td>
<td>53 (27–79)</td>
<td>48 (26–70)</td>
</tr>
</tbody>
</table>

CI, confidence interval.
Discussion

The combination of 5-FU and vinorelbine in advanced breast cancer proved to be active and feasible in many trials [13–15]. In a setting with 5-FU 750 mg/m²/day given as continuous infusion for 5 days and vinorelbine 30 mg/m² intravenously days 1 and 5, 90% of the patients experienced grade 3/4 neutropenia [13].

With 5-FU 350 mg/m²/day days 1–3 and vinorelbine either 25 mg/m² days 1 and 3 or 30 mg/m² days 1 and 3, neutropenia was again the most frequently observed side-effect. A grade 4 nadir occurred in 30 (77%) patients, with four hospital admissions. Thirty-five per cent of those patients had bone metastases [14].

With the new oral fluoropyrimidines like capecitabine, the cumbersome infusional treatment of 5-FU, with its many complications, can be avoided. Some trials have tested the combination of vinorelbine plus capecitabine in metastatic breast cancer. Kattan et al. [16] treated 30 patients with capecitabine 825 mg/m² twice daily days 1–14 and vinorelbine 25 mg/m² days 1 and 8 as first-line chemotherapy for advanced breast cancer. The median age was 54 years, and in 73.5% visceral metastases were present. Four of these patients showed grade 3/4 neutropenia, with one febrile neutropenia. One grade 3 vomiting and one grade 3 mucositis occurred. Welt et al. [17] reported data from 32 patients with a median age of 52 years, who had been pretreated with anthracyclines and/or taxanes, 40% with bone involvement, and found a DLT on the dose level with capecitabine 2000 mg/m²/day days 1–14 and days 22–35 and vinorelbine 25 mg/m² days 1 and 5 and days 22 and 29 out of 42 days. Again, neutropenia was the main toxicity.

In the present trial we tested a regimen with capecitabine and vinorelbine as first-line treatment in a population of patients ≥65 years stratified by bone involvement. No data concerning the toxicity and activity of oral fluoropyrimidines and vinorelbine are available in this population. We did not anticipate overlapping toxicity with this combination, as vinorelbine monotherapy causes mainly hematological and less often neurological side-effects, whereas mucosa and skin toxicity are frequently associated with capecitabine monotherapy. Patients were stratified according to the presence or absence of bone metastases, because we expected more hematological toxicity in patients with impaired bone marrow capacity owing to bone metastases and a higher likelihood of having received radiotherapy before study entry. For patients with bone metastases we had two DLTs at dose level 2 (capecitabine 1250 mg/m² days 1–14 and vinorelbine 20 mg/m² days 1 and 8). The two DLTs were a grade 2 and a grade 3 neutropenia, leading to a dose reduction of vinorelbine on day 8. The recommended dose was thus defined one dose level below, with capecitabine 1000 mg/m² and vinorelbine 20 mg/m².

For patients without bone metastases, two DLTs were observed at dose level 3 (capecitabine 1250 mg/m² days 1–14 and vinorelbine 25 mg/m² days 1 and 8). Both DLTs were due to hematological side-effects: one neutropenia grade 2 on day 8 and one prolonged grade 4 neutropenia. The recommended dose for these patients was therefore at dose level 2.

Our results confirm that elderly patients have a reduced bone marrow tolerance towards the agents studied. In other trials [16, 17], DLTs were mostly hematological drug reactions as well, but at higher dose levels. Patients in these trials were considerably younger (median age 54 and 52 years) compared with our trial population (median age 70 and 73 years). Thus, study results on the tolerability of chemotherapeutic drugs obtained in an average study population with usually younger patients cannot easily be transferred to an average breast cancer population seen in daily practice.

Regarding other organ systems, this regimen was well tolerated, with expected mucosa toxicities but only one grade 3 stomatitis and diarrhea. Asthenia and paresthesia were usually mild to moderate and alopecia could be avoided in most patients, a fact that is often important, especially in this patient population.

Although efficacy was not a primary end point in this trial, antitumor activity was observed at each dose level. The overall response rate was 53% for patients with bone metastases and 48% for patients without. These data are comparable to the response rates found by Noël et al. [14], with a response rate of 49%, and by Welt et al. [17], with a response rate of 52% in the younger study population.

In conclusion, the combination of vinorelbine and capecitabine seems to be an effective first-line treatment for advanced breast cancer, with a tolerable subjective toxicity. Toxicity data obtained from an average breast cancer patient population cannot be extrapolated to an elderly population. Elderly patients need carefully conducted phase I trials to establish an optimal chemotherapy regimen with acceptable efficacy. To obtain more information on the efficacy and tolerability a phase II trial, using the recommended doses found in this phase I part, is currently being conducted by the Swiss Group for Clinical Cancer Research (SAKK).

References


