Purpose. This phase II trial of VEM (vinorelbine + epirubicine + methotrexate) in the treatment of locally advanced breast cancer was conducted to obtain downstaging to allow surgery and breast conservation.

Patients and Methods. This multicenter study recruited 58 patients with locally advanced breast cancer (two patients ineligible); 56 were evaluable for response and tolerance.

Results. Downstaging was obtained in 77% of the patients with a pathological complete response (pCR) rate of 9%. At 33 months of follow-up, median survival has not been reached. Neutropenia grade 3-4 was reported in 31% of cycles with 3% of cycles with infection grade 3. Alopecia grade 3 was noticed for 71% of patients.

Conclusion. VEM represents an effective regimen for patients with locally advanced breast cancer, allowing an important pCR. Moreover, this regimen appears to be particularly well tolerated.

Key Words. Locally advanced breast cancer · Pathological complete response · Conservative surgery · Downstaging

INTRODUCTION

The management of patients with locally advanced breast cancer (LABC) is now seen to require the integration of preoperative (neoadjuvant) chemotherapy and subsequent treatment by surgery or radiotherapy or both, aimed at elimination of residual local disease. This combined modality approach to treatment may be applied with the aim of using the initial chemotherapy to enable a more conservative approach to local control or alternatively, it may be felt that the prime function of the cytotoxic drugs is to eliminate occult distant metastases at a time when resistant clones have not yet emerged [1]. The elements of treatment which are used after initial neoadjuvant chemotherapy should therefore include adequate surgical resection of the primary tumor and regional lymph nodes regardless of the clinical indications of tumor response, together with regional radiotherapy to residual areas at risk of involvement. On the basis of the findings of the pathological appraisal of the surgically resected specimen, an assessment can be made of the need for subsequent adjuvant chemotherapy to further reduce the risks of recurrence.

The choice of cytotoxic drugs selected for neoadjuvant treatment is defined by the activity of the agents in advanced disease, but must also take into account the need to treat patients with early stage disease with a well-tolerated chemotherapeutic combination which will ensure that proceeding to the subsequent surgery is not affected by side effects. Preliminary data relating to a combination of Navelbine® (vinorelbine), epirubicin, and methotrexate suggested that this schedule would be both active and well-tolerated, so it was decided to utilize this regimen to achieve tumor bulk reduction before proceeding to surgery and radiotherapy [2].

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The appropriate selection of drugs for primary treatment must reflect the need to use agents that will achieve both efficient and rapid control of the underlying disease. The most active groups of cytotoxic compounds in the primary treatment of LABC include anthracyclines, active anti-metabolites, and newer classes of agents, such as taxanes, and the new generation of vinca alkaloids. These compounds have been demonstrated to achieve high response rates in advanced disease.

In our previous experience we used cyclophosphamide, doxorubicin, and fluorouracil or epirubicin combinations, which achieved a response rate of 50%, and downstaging in 43% of patients permitting them to proceed to surgical resection of the tumor [3]. Vinorelbine is a semisynthetic second-generation vinca alkaloid and an active drug in the treatment of metastatic breast cancer as a single agent [4-5] or in combination with anthracyclines [6-8], achieving response rates in the range of 40%-60% and 60%-77%, respectively.

Navelbine® combined with epirubicin and methotrexate has been shown to be an effective and well-tolerated regimen in the neoadjuvant treatment of breast cancer; in fact, Van Praagh et al. [2] obtained a response rate of 88% with 14% pathological complete response (pCR) rate, which permitted conservative surgery in 85% of cases for stage II and IIIA patients.

The main purpose of this trial was to obtain downstaging to allow surgery and breast conservation, if possible, in this group of patients with LABC.

**METHODS**

Chemotherapy was administered as initial therapy to patients with breast tumors which were stage III (T any N, M0 or any T N2 M0) disease. The inclusion criteria required patients to have stage IIIA and IIIB disease with the exception of any T, N1, M0 or inflammatory carcinoma (T2). Other requirements for entry to the study included patients aged 18-70 years, with performance status ≤2, life expectancy >3 months and adequate hematological, renal, hepatic, and cardiac function. Patients were excluded if they had evidence of metastatic disease.

All patients gave informed consent. The study protocol conformed to the recommendation of the Helsinki declaration.

The initial clinical evaluation of patients consisted of physical examination together with breast ultrasonography and mammography. Cytological and pathological confirmation of the diagnosis was established by core biopsy or fine needle aspiration (FNA). The presence of distant metastases was excluded by chest x-ray, liver ultrasound, and radionuclide bone scan. Initial laboratory assessment included full blood count, electrolytes, creatinine, transaminases, alkaline phosphatase, and tumor markers carcinoembryonic antigen (CEA) and carbohydrate cell surface antigen (CA) 15-3.

The following treatment schedule was administered: vinorelbine 25 mg/m²; epirubicin 35 mg/m²; methotrexate 20 mg/m² given at day 1 and day 8 every 28 days for four courses after which response was assessed.

Toxicity was evaluated also according to World Health Organization (WHO) criteria by clinical and laboratory evaluations at day 28 of each cycle, and a complete blood cell count was performed weekly. All patients underwent electrocardiogram (ECG) and left ventricular ejection fractions (LVEF) before study entry, and ECGs were repeated before each course and at the end of treatment. Furthermore, resting ventricular ejection fractions were regularly determined by echocardiography.

Responding patients received two more cycles and then proceeded to appropriate surgical resection and radiotherapy.

Patients with stable disease received two more cycles and if a response was achieved, they proceeded to surgery and radiotherapy; if there was no response after six cycles, radiotherapy alone was administered (Table 1; Fig. 1). Patients with progressive disease were withdrawn from the study. The evaluation of response after primary chemotherapy utilized the WHO criteria, but pathological response in the surgically resected specimen was based on detailed microscopic examination of multiple sections from the breast and axillary lymph nodes. All responses and major toxicities were reviewed by a panel of oncologists.

All patients were considered to be assessable for response and toxicity in intent-to-treat rules. Patients were stratified into two groups according to stage: IIIA and IIIB. Disease-free survival was measured from the initiation of treatment until relapse and overall survival from the initiation of treatment until patient death. Survival was estimated using the Kaplan-Meier method. Tolerance and response rates were analyzed by descriptive methods.

**RESULTS**

Fifty-eight patients were accrued to the study between June 1995 and June 1996. Two patients were stage IIB (ineligible), and 25 and 31 patients were at IIIA and IIIB, respectively. The patient distribution according to T classification is described in Table 2. The average tumor diameter by clinical evaluation was 61 mm (range: 19-100) for the first group and 51 mm (range: 20-130) for the second group. The median age of the patients was 50 years (range 32-65 years) and 27 of the patients were premenopausal.

Fifty-eight patients received a median of four cycles (range two to six) of therapy. In total, 266 courses were administered, with dose intensities of 99% of scheduled dose
VEM as Primary Treatment in Locally Advanced Breast Cancer

for Navelbine®, 98% of the planned dose for epirubicin, and 99% of the programmed dose for methotrexate.

The toxicities associated with therapy are summarized in Table 3. Hematological toxicity at grade 3-4 was predominantly related to neutropenia (31% of cycles) but only resulted in grade 3 infection in 3% of cycles; the other principal nonhematological toxicity was alopecia at grade 3 in 71% of patients. WHO grade 1/2 fever without signs of infection was experienced by 14% of patients. No withdrawals due to toxicity or toxic deaths were observed in this trial.

Clinical evaluation of the efficacy of VEM (vinorelbine + epirubicin + methotrexate) showed that downstaging was achieved for 77% of patients but after pathological examination of the resected specimens, pCR of all evidence of malignancy was documented in 9%. Downstaging and pCR rates were equivalent for stage IIIA and IIIB. The surgical procedures applied are shown in Table 4. As expected,

Table 1. Patient characteristics

<table>
<thead>
<tr>
<th></th>
<th>All</th>
<th>Stage IIIA</th>
<th>Stage IIB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients eligible</td>
<td>56</td>
<td>25</td>
<td>31</td>
</tr>
<tr>
<td>Age (years) median range</td>
<td>50</td>
<td>49</td>
<td>51</td>
</tr>
<tr>
<td>WHO performance status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>37</td>
<td>17 (68)</td>
<td>20 (65)</td>
</tr>
<tr>
<td>1</td>
<td>19</td>
<td>8 (32)</td>
<td>11 (35)</td>
</tr>
<tr>
<td>Hormonal status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Post-menopausal</td>
<td>29</td>
<td>15 (60)</td>
<td>14 (45)</td>
</tr>
<tr>
<td>Premenopausal</td>
<td>27</td>
<td>10 (40)</td>
<td>17 (55)</td>
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<tr>
<td>Receptor status</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- estrogen receptor (ER+)/PgR*</td>
<td>8 (14)</td>
<td>1 (4)</td>
<td>7 (23)</td>
</tr>
<tr>
<td>- ER+/PgR*</td>
<td>9 (16)</td>
<td>1 (4)</td>
<td>8 (26)</td>
</tr>
<tr>
<td>- ER-/PgR*</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>- ER+/PgR*</td>
<td>2 (4)</td>
<td>1 (4)</td>
<td>1 (3)</td>
</tr>
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<td>- Unknown</td>
<td>37 (66)</td>
<td>22 (88)</td>
<td>15 (48)</td>
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<tr>
<td>SBR*</td>
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<td>1 (3)</td>
</tr>
<tr>
<td>2</td>
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<tr>
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<td>11 (20)</td>
<td>4 (16)</td>
<td>7 (23)</td>
</tr>
<tr>
<td>Unknown</td>
<td>28 (50)</td>
<td>17 (68)</td>
<td>11 (35)</td>
</tr>
</tbody>
</table>

*Scarf-Bloom-Richardson grade
WHO = World Health Organization

Table 2. T distribution according stage

<table>
<thead>
<tr>
<th>Stage/T</th>
<th>T1</th>
<th>T2</th>
<th>T3</th>
<th>T4</th>
<th>Median tumor size (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IIIA</td>
<td>2 (7%)</td>
<td>23 (40%)</td>
<td>0</td>
<td>0</td>
<td>61</td>
</tr>
<tr>
<td>IIB</td>
<td>2 (7%)</td>
<td>21 (3%)</td>
<td>2 (36%)</td>
<td>6 (10%)</td>
<td>51</td>
</tr>
</tbody>
</table>

*T4a, b or c = missing data
more patients (24%) with stage IIIA have had a partial mastectomy compared to stage IIIB patients (10%). Median and disease-free survival have not been reached at 33 months of follow-up. Eight patients (5 and 3 stage IIB-IIIA and 3 stage IIIB group, respectively) have died due to disease.

**DISCUSSION**

The primary treatment of locally limited breast cancer is locoregional treatment that most often consists of conservative surgery combined with radiation. A breast-sparing operation is the therapeutic method of choice for removing unifocal, invasive tumors as long as they do not involve the margins of the incision, but conservative surgery is generally recognized only to be appropriate for tumors of up to 4 cm in diameter; in no case should the surgeon perform this procedure in bigger tumors (>5 cm).

The intention of treating patients with high-risk local disease by combined modality therapy is both to ensure control of the primary tumor and also to minimize the risk of subsequent distant metastases. The relative contribution of the initial chemotherapy has been felt to relate equally to its impact on the identified bulk of disease and also in preventing occult distant metastases. The measurable impact on disease-free survival is similar to that which can be achieved with adjuvant chemotherapy administered after primary management [9]. Neoadjuvant treatment achieved downstaging of the locoregional tumor involvement even in patients with extensive disease at presentation (T2 or T3) [10]. The selection of patients who would benefit from partial or complete surgical resection remains difficult, and the finding of histological evidence of residual active tumor in the great majority of resected specimens confirms the need for caution.

In patients with locally advanced technically operable cancer (IIIA), total or radical mastectomy has been the therapeutic method of choice for decades while with technically inoperable cancer (IIIB), the method of choice was radiotherapy with subsequent mastectomy. This approach has had no effect on the 5-year survival rates, and it has not been until the advent of primary chemotherapy that the outcome has improved. There is no doubt that the main problem of locally advanced cancer (in addition to the primary tumor per se) is the presence of the anticipated micrometastases formed months, perhaps years, before presentation. As a result, systemic chemotherapy combined with locoregional methods would seem to be the most effective approach. Neoadjuvant, i.e., primary chemotherapy, is intended to reduce the primary tumor and/or nodes (downstaging), improve operability, and allow consideration of breast-sparing operations (lumpectomy, segmentectomy, quadrantectomy), i.e., conservative surgical procedures. Another goal of primary chemotherapy is to destroy presumed and objectively undetectable micrometastases, while the ultimate intention, in addition to sparing the breast, is to extend the tumor-free interval and overall survival [11]. The results of primary chemotherapy (CMF, FAC, and FEC regimens) published by the Milan group [12-14] and by other authors [15-17] have established the activity of this approach, and
the results of treatment of advanced breast cancer using vinorelbine-based combination therapy, even as first-line therapy [3, 5, 7] are also known. Logically, a cytotoxic agent effective in disseminated disease will also be effective in locally advanced disease with anticipated micrometastases. As a result, just as other authors transferred combination regimens (CMF, FAC, FEC) found to be effective and tested as adjuvant therapy and in disseminated cancer to primary therapy, we used the VEM regimen in the same indication (i.e., primary therapy).

In the Czech Republic, a total of 4,500 women are diagnosed to have breast cancer each year (83.3/100,000 population). Almost 40% of the patients present with the disease in an advanced stage at the time of diagnosis and locally advanced cases are common, so the most frequent surgical procedures are mastectomy with axillary dissection. The aim of our study was to test, among other things, the potential of conservative surgical procedures following primary chemotherapy. The proportion of positive results we achieved in terms of downstaging (77%) is comparable with the results reported by other authors [18-19], as is the proportion of complete pathological remissions achieved (pCR = 9%). But despite these promising results, a conservative surgical procedure was performed in as few as 16% of cases.

Surgeons (and also some oncologists) have been accustomed to observing the unavoidable progression of the disease in what was originally locally advanced cancer and have been reluctant to acknowledge the benefits of a conservative operative approach despite the very good results of primary chemotherapy. Since 1995, when our study was launched and we started to publish our data, there has been a gradual change in these attitudes, and conservative surgery following primary successful chemotherapy is now generally accepted and practiced. It goes without saying that the policy is complemented with radiotherapy where indicated and adjuvant cytotoxic and, possibly, hormonal therapy. Interestingly, only eight patients out of a total of 58 have died at 3 years after completion of the study; the other patients are alive and although this result is also encouraging and comparable to the experience of others, it will take some time before long-term data will be available.

For verification, the inclusion criteria of our study also allowed, besides “core biopsy” or “incision biopsy,” FNA biopsy. Using these biopsy specimens, it was usually impossible to identify hormonal receptors, which explains the relatively high number of patients with unverified hormonal receptors. This finding led us to formulate the rule, as a methodological guideline, not to use FNA for pathological verification before primary chemotherapy.

The employed VEM combination was very well tolerated by the patients. We did not notice any infectious complications, any serious cardiovascular toxicity or any changes in LVEF. Leukopenia and neutropenia (grade IV in two and seven cases, respectively) were managed by standard measures and did not require any special hospitalization regimen. The most common toxic symptom was complete alopecia (71%). This effect, most stressful and depressing for the patient, had no impact on the therapeutic procedure and was eventually overcome by standard procedure (wig). None of the above toxic symptoms (Table 3) required discontinuation or delay of treatment.

It can thus be reasonably concluded that the combination we used turned out to be both effective and well tolerated in primary therapy of advanced breast cancer. When compared with the other protocols employed in the same indication, it is at least as effective and even superior to them based on the absence of cardiotoxicity. Last but not least, it is less costly compared with the recently tested neoadjuvant regimens (e.g., taxane-based regimens).

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