Gemcitabine and Oral Vinorelbine as Salvage Treatment in Patients with Advanced Anthracycline- and Taxane-pretreated Breast Cancer

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Abstract. *Background: Despite progress achieved with new chemotherapeutic and endocrine agents, advanced breast cancer (ABC) remains a disease with poor prognosis. We sought to determine the efficacy of gemcitabine (GC) and oral vinorelbine (VB) in heavily preatreated ABC. Patients and Methods: Patients previously treated with anthracyclines and taxanes in the metastatic setting with progressive disease were eligible. Treatment consisted of VB (60 mg/m^2, orally) and GC (1000 mg/m^2, intravenous infusion), every two weeks of a 28-day cycle. Results: Thirty-one patients with ABC were enrolled. Toxicity was acceptable, mainly haematological. Three and 8 patients achieved a complete (9.6%) and partial (25.8%) response, respectively; ten patients (32.2%) had stable disease. Median time-to-progression was 5.3 months, while in responders 8.6 months. Median overall survival was 14 months. Conclusion: Oral VB and GC is an active and well-tolerated combination in anthracycline/taxane-pretreated ABC, representing an interesting option in this poor prognosis group of patients.*

Advanced breast cancer (ABC) remains incurable despite the progress achieved in recent decades. The current standard approach for ABC patients includes taxane- and anthracycline-based regimens, while other agents may also have an important role in other groups of patients. Although the administration of new chemotherapeutic and endocrine agents has improved the other survival variables such as time-to-progression, prognosis remains poor in ABC and no single therapy has been demonstrated to substantially prolong survival (1). Therefore, the main goal of therapy is actually palliation and quality of life improvement.

Gemcitabine (GC) is an antimetabolite with a particular mode of action; it becomes incorporated and inhibits the elongation of nascent DNA strands. It also inhibits ribonucleotide reductase, an enzyme producing the deoxynucleotides required for DNA synthesis (2). Vinorelbine (VB), a semisynthetic vinca alkaloid, is a cell-cycle specific agent and blocks cells in mitosis through its ability to bind specifically to tubulin and to block the ability of the protein to polymerize into microtubules. Due to its lower effect on axonal microtubules, it is substantially less neurotoxic than native vinca alkaloids (3). Experimental and clinical data in lung cancer suggest an additive effect of the two drugs (4-5).

GC as a single agent has a response rate of approximately 20% in ABC (6-7). Single-agent activity of VB in the same disease is higher, with response rates of 35-41% in first-line and 15-30% in second line treatment (8-11). GC and intravenous VB in combination had a response rate of approximately 22-54% in ABC (12-18). The main toxicity of both drugs is haematological toxicity.

After the introduction of VB oral formulations various studies were conducted to compare the characteristics of oral and intravenous forms (19-20). The absolute bioavailability of oral VB (soft gelatine capsule) was close to 40%. Pharmacokinetic/pharmacodynamic (PK/PD) behaviour and safety profiles were comparable for both oral and intravenous routes, while the inter-individual variability in drug exposure was also equivalent. Reliable, corresponding doses between oral and intravenous VB were established of 80 mg/m^2 *versus* 30 mg/m^2 and 60 mg/m^2 *versus* 25 mg/m^2, respectively. Since intravenous VB is also associated with significant venous reactions, local phlebitis is a common problem, in some cases preventing the completion of the chemotherapy plan or necessitating costly central venous access and hopitalization. Conversely, gastrointestinal toxicity (vomiting, constipation, nausea, diarrhoea) are slightly higher with the oral VB, although generally mild.

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Table I. *Patient demographic and clinical data.*

Patients	31
Age (years)	
median	54
range	31-74
Performance status (ECOG)	
0	8 (25.8%)
1	14(45.16%)
2	9 (29.03%)
Metastatic sites	
bones	12
brain	6
liver	14
lung	8
soft tissue	9
other (nodes, other breast, *etc.*)	6
Previous treatment for advanced disease	
one chemotherapy line	21 (67.74%)
two chemotherapy lines	10 (32.25%)
hormone therapy	18 (58.06%)
palliative radiotherapy	9 (29.03%)

Table II. *Haematological and non-haematological toxicities according to WHO.*

Toxicity/ Grade	1	2	3	4
Haematological				
Anemia	12 (38.7%)	4 (12.9%)	0	0
Leukopenia	18 (58.06%)	3 (9.67%)	1 (3.22%)	0
Neutropenia	16 (51.61%)	3 (9.67%)	1 (3.22%)	0
Thrombocytopenia	10 (32.25%)	2 (6.45%)	1 (3.22%)	0
Non-haematological				
Alopecia	7 (22.58%)	2 (6.45%)	0	0
Constipation	9 (29.03%)	3 (9.67%)	0	0
Diarrhea	1 (3.22%)	4 (12.9%)	0	0
Fever	11 (35.48%)	3 (9.67%)	0	0
Nausea/Vomiting	17 (54.83%)	4 (12.9%)	1 (3.22%)	0
Neurosensory	3 (9.67%)	2 (6.45%)	0	0
Phlebitis	3 (9.67%)	1(3.22%)	0	0

We sought to assess the activity of a combination of GC and oral VN as salvage therapy for ABC patients progressive after anthracycline and taxane chemotherapy in the metastatic setting, a clinical condition often associated with exhausted organ reserves and venous access. To our knowledge this is the first study that evaluates the combination regimen of gemcitabine and oral vinorelbine in pretreated ABC.

Patients and Methods

Eligibility criteria. Patients with histologically confirmed advanced breast cancer, age >18 years, ECOG performance status 0-2, life expectancy >3 months, adequate bone marrow reserve (WBC count ≥3.500/μL,neutrophils ≥2.000/μL, hemoglobin ≥10 g/L, platelet count ≥100.000/μL), adequate liver and renal function (serum bilirubin ≤1.5 mg/d L,AST and ALT <3x upper limit of normal, and serum creatinine ≤2 mg/dL) were eligible. Cases with the presence of any secondary malignancy were excluded. This combination treatment was approved by the local ethics comitee and an informed consent was obtained from the patients before the administration of therapy.

Assessment of response and toxicity. Before entry, all patients underwent the following evaluations: medical history, physical examination, tumor evaluation – measurement and staging, WHO performance status, ECG, complete blood cell count, serum chemistries, liver and renal function tests, serum tumor 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. Response and toxicity were assessed using the standard WHO criteria. Time to progression and survival was measured from the day of the first dose of chemotherapy.

Treatment plan. Treatment consisted of VB (60 mg/m^2, administered orally) and GC (1000 mg/m^2, administered intravenously), every two weeks (on days 1 and 15) of a 28-day cycle. In cases of myelotoxicity, dose adjustments and treatment postponements were conducted based on complete blood cell count and clinical assessment. Patients who showed progression discontinued treatment after at least 3 courses. Patients with stable disease or response continued treatment for up to six cycles (6 months) and further therapy was at the discretion of the oncologist. During therapy, tumor evaluation was conducted every three cycles, and after completion of the treatment plan follow-up was performed every three months.

Results

Thirty-one patients with ABC were enrolled between June 2004 and January 2006. The patients' demographic and clinical data are shown in Table I. All patients were previously treated with anthracyclines and 23 (74.1%) had also received taxanes in the metastatic setting and presented with progressive disease.

Three patients achieved a complete response (9.6%) and 8 patients (25.8%) achieved a partial response. Response seemed to be higher in patients with lung and soft tissue metastasis and lower in patients with liver metastases. Ten patients (32.2%) had stable disease and ten patients (32.2%) had progressive disease. The median time to progression was 5.3 months overall (95% CI, 1.1-16 months) and 8.6 months in responding patients (95% CI, 3.2-16 months). Median overall survival was 14 months (95% CI, 1.4-19 months).

Haematological and non-haematological toxicities were mild to moderate. Leukopenia, nausea and vomiting were the most common toxicities. The major toxicities are summarized in Table II.

Discussion

The majority of patients with breast cancer receive anthracycline/taxane based chemotherapy either in the adjuvant or the metastatic treatment. The regimens administered to pretreated advanced breast cancer patients should therefore contain drugs without complete clinical cross-resistance with either anthracyclines or taxanes; they should also have low toxic potential and non-cross resistance between each other. Both VB and GC are active as single agents in breast cancer and have the aforementioned characteristics.

The administration of VB and GC in non-small cell lung and bladder cancer, on day 8 seems to enhance the grade 3 and 4 myelotoxicity, rather than improving the efficacy, resulting in treatment delays or dose reductions (21-22). We therefore decided to administer both drugs every two weeks. Moreover, given the high incidence of venous access "exhaustion" in heavily pretreated ABC, we opted to substitute intravenous for oral VB in equivalent doses recommended for combination therapy (60 mg/m^2).

Response rates with the combination of both drugs intravenously range between 22 and 54% in the reviewed literature (12-18). The 35.4% response rate as well as the 32.2% of disease stabilization, observed in the present study are similar or better than those of the above reports.

The combination was in general well-tolerated; toxicity was mild, mainly neutropenia. Non-haematological toxicities were minimal and transient. The oral formulation of VB is more feasible and convenient with much less venous toxicity than that observed with the intravenous formulation.

Oral formulations of anticancer drugs have several advantages over intravenous administration. They do not require intravenous access, so reactions at the injection site and local phlebitis are eliminated and they offer both quality of life and health care cost advantages. Therefore, patient convenience and preference and the pharmacoeconomic issues justify further clinical development of anticancer oral formulations.

The administration of oral vinorelbine and gemcitabine is an active, well-tolerated combination and may represent a reliable salvage option in breast cancer patients failing anthracyclines and taxanes. Yet, the combination of gemcitabine / oral vinorelbine with newer targeted agents may further improve the outcome of ABC.

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