

Mitomycin C and vinblastine: an active regimen in previously treated breast cancer patients

Inna Ospovat¹, Nava Siegelmann-Danieli², Tal Grenader¹, Ayala Hubert¹, Tamar Hamburger¹, and Tamar Peretz¹

¹Department of Oncology, Hadassah University Hospital, Jerusalem; ²Maccabi Health Organization, Tel-Aviv, Israel

ABSTRACT

Background. Metastatic breast cancer has a substantial mortality burden on women worldwide. Presented herein is our experience with the combination of mitomycin-C and vinblastine in heavily pretreated breast cancer patients.

Methods. Candidates were women with measurable metastatic disease, previously exposed to two or more chemotherapy regimens. Mitomycin-C was given at the dose of 10 mg/m² on day 1 and vinblastine at 6 mg/m² on days 1 and 21 of each 42-day cycle. Analysis included patients exposed to one or more cycles of therapy. Kaplan-Meier curves were used to generate overall survival and time-to-treatment progression curves.

Results. Forty patients previously exposed to a median of three prior regimens were included. Partial response and stable disease were reported in 14 (35%) and 10 (25%), patients, respectively, for a clinical benefit of 60%. With a median follow-up of 11 months, the median time to progression and survival durations lasted 4 and 12 months, respectively. In a subgroup of 17 women with prior anthracycline and taxane exposure, partial response and stable disease were reported in 4 (23.5%) and 5 (29%), respectively. Treatment was generally well tolerated, with grade 3-4 hematologic and non-hematologic toxicity reported in 8 (20%) and 3 (7.5%) patients, respectively. Two cases of fatalities (5%) occurred with pulmonary toxicity in women heavily exposed to mitomycin-C (cumulative doses of ≥ 40 mg/m²) and soon after red blood cell transfusion.

Conclusions. Chemotherapy with mitomycin-C and vinblastine is active and well-tolerated in heavily pretreated breast cancer patients. Caution should be taken to avoid blood transfusion alone with mitomycin-C therapy.

Introduction

We describe herein our experience with the combination regimen of mitomycin-C (MMC) and vinblastine (VBL) in a modern series of heavily pretreated metastatic breast cancer patients. Most breast cancer patients are today diagnosed with early stage diseases. Still, a substantial proportion will eventually relapse and ultimately die of metastatic disease¹. Anthracyclines and taxanes, long considered the preferred cytotoxic chemotherapy agents in metastatic disease, have now been moved to the adjuvant setting. There is therefore a need to explore additional efficacious well-tolerated regimens to be offered at the time of relapse. The MMC/VBL combination has long been used in patients with metastatic disease prior to the taxane era. It has been shown to be moderately effective and generally well tolerated and is relatively inexpensive²⁻⁸.

Presented herein is our experience with the MMC/VBL combination regimen to suggest its potential role in modern oncology.

Key words: breast cancer, mitomycin-C, vinblastine.

Correspondence to: Inna Ospovat, MD, Department of Oncology, Hadassah University Hospital, PO Box 12000, 91120 Jerusalem, Israel.
Tel 972-2-6777825;
fax 972-2-6777388;
e-mail innaospovat@gmail.com

Received August 25, 2008;
accepted March 25, 2009.

Methods

Patients Candidates were women with documented measurable metastatic disease and a histological diagnosis of primary breast cancer. All patients received at least two prior cytotoxic regimens in the adjuvant and or metastatic setting. Addition eligibility criteria included performance status 0-2, age ≥ 18 years, and adequate bone marrow, liver and kidney reserves.

Treatment The combination regimen consisted of MMC at 10 mg/m² IV on day 1 and VBL at 6 mg/m² IV on days 1 and 21 of a 42-day (6 weeks) cycle. Treatment was delayed for recovery if white blood cell count was less than 3.0×10^9 and/or platelets below 100×10^{12} for up to 2 weeks. Symptomatic anemia was treated with red blood cell transfusion. A 10-20% dose reduction followed low bone marrow tolerability.

Tumor response assessment The evaluation of response referred to reports of physical examination and imaging studies with chest roentgenography, computerized tomography scans and abdominal ultrasound performed at least 6 weeks apart. Blood tests with liver function and tumor markers and imaging with bone scans were considered to exclude disease progression. Response was assessed according to the standard WHO criteria⁹. Briefly, complete response was assigned for the disappearance of all known disease, partial response for 50% or greater decrease in the sum of the products of the largest perpendicular diameters of all measurable lesions, stable disease if <50% decrease and <25% increase in the sum of the products of the largest perpendicular diameters of all measurable lesions occurred, and progressive disease as a >25% increase in the size of any target lesion or the development of new metastases. For patients responding with a complete or partial response, the response had to be documented for at least an additional 4 weeks of follow-up.

Adverse events were classified according to the Common Toxicity Criteria of the National Cancer Institute¹⁰.

Statistical analysis Duration of follow-up, time to tumor progression (TTP), and overall survival were measured from day 1 of the first MMC/VBL cycle to the sensing event. All patients receiving at least one full cycle of therapy were included for analysis. Survival curves were estimated according to the Kaplan-Meier method. Logistic regression models were also used to identify clinically significant prognostic factors.

Results

Patient characteristics

Forty female patients with measurable metastatic disease were included for analysis (Table 1). The median age at enrollment was 52 years (range, 32-74), and the median number of prior chemotherapy regimes was 3

Table 1 - Patient characteristics

	No. of patients	%
Total	40	100
Age, yr, mean	51.9	
ER status		
Positive	15	37
Negative	10	25
Unknown	15	37
Site of metastases		
Bone	20	50
Lung	10	25
Liver	6	15
Local	10	25
Lymph	4	4
More than 2 sites	9	22.5
No. previous treatment regimens		
1-2	18	45
3-6	22	55
Prior anthracyclines	20	50
Prior taxanes	18	45
Prior taxanes & anthracyclines	17	42.5

(range, 2-6). Two or more sites of metastatic disease were documented in 9 women (22.5%). Thirty-three patients (82.5%) relapsed following initial therapy for operable tumors. The median interval between diagnosis and relapse was 27.5 months (range, 2-242).

Treatment outcome

The median duration of MMC/VBL therapy was 10.5 weeks (range, 6-48). Fourteen patients (35%) had a partial response and an additional 10 patients (25%) had stable disease lasting 4 or more months, for a clinical benefit of 60%. With a median follow-up of 11 months (range, 2.5-49), the median TTP and overall survival durations were 4 (range, 1.5-23) and 11 months (range, 9-13), respectively. One- and two-year overall survival rates were 39.4% and 15.7% respectively.

In a subgroup of 17 patients previously exposed to both anthracyclines and taxanes, partial response was noted in 4 women (23.5%) and stable disease lasting 4 or more months in 5 (29%). Median TTP and median overall survival durations lasted 3 (range, 2-7) and 11 months (range, 3-38 months), respectively.

TTP was significantly longer in women exposed to only two prior regimens than in those exposed to three or more (medians of 5 *vs* 3 months, respectively, $P = 0.02$, Figure 1). It was significantly shorter with early relapsing disease (less than 24 months) than with late relapse (medians of 3 and 5 months, respectively, $P = 0.04$) and in women with than in those without liver metastases (medians of 1.5 *versus* 4 months, respectively, $P = 0.048$). Patients with hormone-responsive tumors and of a younger age responded for longer periods than non-hormone-responsive and older women, although differences were not statistically significant.

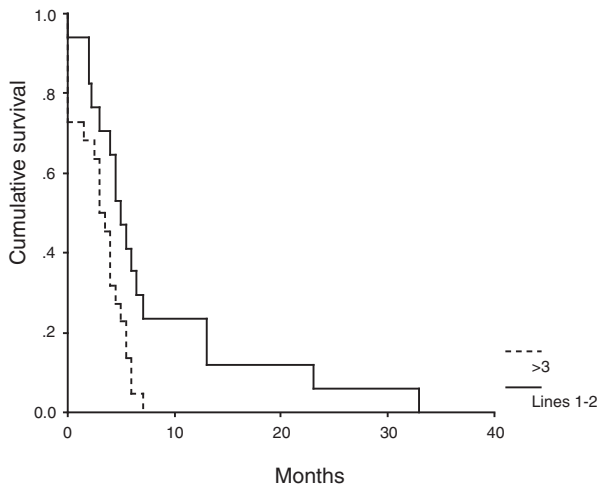


Figure 1 - Time to progression of patients with 1-2 previous lines of treatment versus 3 or more previous lines of treatment.

Toxicity

Therapy was generally well tolerated and toxicity manageable; adverse events are summarized in Table 2. Grade 3-4 hematology and non-hematology toxicities were recorded in only 8 (20%) and 3 (7.5%) patients, respectively. Gastrointestinal-related toxicities (constipation, abdominal pain, vomiting) were the most common, although most were of a low grade. There were two fatalities (5%) secondary to pulmonary toxicity (adult respiratory distress syndrome) in women exposed to multiple doses of MMC (cumulative MMC dose of 40 and 133 mg/m², respectively) that occurred soon after (within 24 hr) red blood cell transfusion.

Discussion

Identification of well-tolerated, effective and inexpensive treatment options for patients with metastatic breast cancer is an ongoing clinical challenge. These patients survive for a median of 2-3 years¹¹. Patient management is mostly palliative, and treatment should be well tolerated. The combination regimen of MMC and

VBL has established its role in metastatic disease, mostly prior to the taxane era. It had been shown to be moderately effective, well tolerated and relatively inexpensive (Table 3)³⁻⁶.

In the current work, we present data suggesting a role of the MMC-VBL regimen in modern oncology, with overall response rate of 35% and a clinical benefit of 70% in patients exposed to a median of three prior cycles. More importantly, responses of 52%, a TTP of 4 months, and an overall survival of 11 months were noted in a subgroup of women with prior exposure to both anthracyclines and taxanes. These results compare favorably with those reported with gemcitabine and vinorelbine (response of 36%, TTP of 6 months, and overall survival of 15.9 months)¹² and more recently with those reported for treatment with ixabepilone with capecitabine (response rate 34.7% and progression-free survival of 5.8 months)¹³. However, our data should be interpreted with caution, given the retrospective nature of our report.

It is noteworthy that in our study, only 42% of the patients had previously received treatment with taxanes and anthracyclines, due primarily to an unwillingness to accept alopecia. In addition, the fact that only 40% of the patients had visceral disease was a reflection of existing recommendations to use MMC and VBL with caution in patients with abnormal liver function and an awareness of the increased risk of pneumonitis when the drugs are administered concomitantly. For these reasons, the combination was not given to patients with liver disease, or those with lymphangitic spread and massive metastatic involvement of the lungs.

The toxicity profile of the MMC-VBL regimen was generally favorable and in accord with prior assessments of the regimen. However, fatal pulmonary toxicity occurred in 2 patients (5%) in our series and was likely related to the administration of MMC followed within 24 hr by red blood cell transfusion. Pulmonary toxicity is one of the most serious side effects of MMC and has been reported at various severities in 2-38% of patients exposed to the drug¹⁴. Potential precipitating factors include: high oxygen concentration, co-administration of vinka alkaloids, blood transfusion, radiotherapy, and elevated cumulative dose (above 60 mg/m²). The pathogenesis is not completely understood and may be asso-

Table 2 - Incidence of toxicity

Toxicity	Who grade I-II No. (%)	III-IV No. (%)
Anemia	1 (2.5)	5 (12.5)
Thrombocytopenia	2 (5)	3 (7.5)
Neutropenia	0	0
GI side effects	7 (18.5)	0
Other	1 (2.5)	3 (7.5)
Late fatal complications	2 (5)	

Table 3 - Comparisons with other studies³⁻⁶

	OR (%)	TTP (mo)	Toxicity (%)	No. of patients	No. of lines
Present study	35	4	20	40	2-6
Garewal <i>et al.</i> ³	35	6	10	48	3-4
Radford <i>et al.</i> ⁴	22	n.d.	mild	49	3-4
Sedlasek ⁵	34 (82)	n.d.	13	35 (11)	3-4
Perrone <i>et al.</i> ⁶	11.5	3.5	50	26	2-3

OR, overall response; TTP, time to progression.

ciated with immune-related endothelial injury by the alkylation of DNA, alveolar macrophage stimulation and cytokine release¹⁵. This adverse event been reported to start within a few hours and up to 3-6 weeks from the last MMC dose and includes bronchospasm, acute pneumonitis alone or with hemolytic-uremic-like syndrome, chronic pneumonitis, and rarely pleural disease. It may respond to corticosteroid therapy¹⁴⁻¹⁹. A physician administering MMC should be aware of this toxicity, avoid red blood cell transfusion (may suggest erythropoietin when needed), and limit MMC cumulative exposure to 60 mg/m²²⁰.

In conclusion, MMC/VBL is a well-tolerated and moderately effective regimen in a modern series of heavily pretreated metastatic breast cancer patients, including those with prior exposure to anthracyclines and taxanes. Its prospective benefit should be considered.

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