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M-VAC (Methotrexate, Vinblastine, Doxorubicin and Cisplatin) for Advanced Carcinoma of the Bladder

The French Federation of Cancer Centers Experience

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70 patients with advanced transitional cell carcinoma of the bladder received methotrexate, vinblastine, doxorubicin and cisplatin (M-VAC). Complete responses (CR) were obtained in 13 of the 67 (19%) evaluable patients and partial responses (PR) in 25 patients for an objective response rate of 57% (95% CI 45–69%). Of the 54 patients who have had a minimum follow-up of 2 years, 8 patients (15%) are disease-free or have stable residual disease. Median survival of the 70 patients was 13 months. Toxicity was acceptable with no drug-related deaths. Because of myelosuppression, only 15 patients (21%) received treatment without delays in drug administration or modifications from the planned schedule. Our results confirm that this regimen is effective, with some patients being long-term survivors.
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INTRODUCTION

BLADDER CANCER is an important cause of death in France, with the French Cancer Registry estimating that there were 8000 new cases diagnosed and 3700 deaths resulting from this tumour in 1982 [1]. Patients with metastatic bladder carcinoma could expect a short survival and a universally fatal outcome in the era before the availability of cisplatin-based chemotherapy [2]. Since cisplatin has been available to treat bladder carcinoma, high response rates and frequent complete remissions have occurred [3, 4].

In 1985, Sternberg and associates reported a high tumour response rate in 25 patients with advanced transitional cell carcinoma of the urothelium treated with the chemotherapy regimen using methotrexate, vinblastine, doxorubicin and cisplatin (M-VAC) [5].

We report our experience with this regimen, where we treated 70 patients with advanced transitional cell carcinoma of the bladder, between January 1986 and June 1989, at five different cancer centres.

PATIENTS AND METHODS

Eligibility

Criteria for eligibility included biopsy showing proven transitional cell carcinoma of the bladder, metastatic and/or locally advanced unresectable disease, bidimensionally measurable disease on physical examination or imaging procedures, World Health Organisation (WHO) performance status of 3 or less, creatinine clearance over 50 ml/min, leucocytes above 4000/μl, platelets over 100 000/μl and serum bilirubin under 2 mg/dl. Prior chemotherapy was allowed.

Treatment

The chemotherapy was administered intravenously in monthly cycles according to the schedule described by Sternberg *et al.* [5]. Methotrexate 30 mg/m^2 was given on day 1; vinblastine 3 mg/m^2, doxorubicin 30 mg/m^2 and cisplatin 70 mg/m^2 were administered on day 2. Cisplatin was given in 250 ml NaCl 3% with a forced diuresis induced with hyperhydration and mannitol. Methotrexate 30 mg/m^2 and vinblastine 3 mg/m^2 were repeated on days 15 and 22. Antiemetics usually consisted of metoclopramide 3 mg/kg and clorazepate 30 mg.

As a dose modification, methotrexate and vinblastine were given on day 15 and 22 only if the white blood count was greater than 2500 μl and no mucositis was present. On day 1, treatment was delayed weekly if patients had not recovered from toxicity. Methotrexate and cisplatin were withheld if creatinine clearance was under 40 ml/min.

The received dose intensity for each patient was calculated and was expressed as a percentage of that intended [6].

Evaluation

All patients were assessed initially by a complete history and physical examination, haematological and liver function tests, serum creatinine, creatinine clearance, chest X-ray, bone scan, ultrasonography and/or CT of the abdomen and pelvis. Patients who had not had a prior cystectomy underwent cystoscopy and examination under anaesthesia before initiation of chemotherapy. Before each treatment, a physical examination, complete blood count and serum chemistry were performed. Appropriate radiological investigations were repeated every two to three cycles. For patients achieving a complete response (CR), the chemotherapy was stopped after six cycles. Patients with a

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partial respone (PR) were continued on chemotherapy until CR or disease progression was noted.

For the bladder to be designated as a site of CR required that both biopsy and cytology results be negative. No surgical staging was attempted.

End points

Treatment endpoints were defined as response rate, duration of response, survival and toxicity. Response was assessed after a minimum of two cycles of treatment according to the following criteria: CR = complete disappearance of all symptoms and signs of disease for a minimum of 4 weeks. Bone abnormalities were required to show evidence of healing on bone scan; PR = a 50% reduction in the sum of the products of the perpendicular diameters of all measurable disease and no appearance of new malignant lesions.

Stable disease (SD)—was a less than 50% decrease or less than 25% increase in the sum of the products of the diameters of all measurable disease for a minimum of 8 weeks; progressive disease (PD)—when a greater than 25% increase in the sum of the products of the diameters of all measurable disease or the appearance of new lesions was evident.

The duration of response was measured from the date of documented response for the CR and from the beginning of the treatment for the PR according to the WHO criteria [7]. Survival was calculated from the date of initiation of chemotherapy by the method of Kaplan and Meier [8].

Differences within groups were determined by the χ^2 with Yate's correction. Toxicity was recorded according to the WHO criteria [7].

RESULTS

Characteristics of patients

70 patients were entered into the study; 1 patient was lost to follow-up after one cycle, 1 patient refused any further evaluation after receiving the first cycle and 1 patient died of hepatic failure 4 weeks after the start of the treatment, leaving 67 patients evaluable for response.

Patient population characteristics are summarised in Table 1. The median age was 57 years. The male to female ratio was 9.0:1.0. All patients had transitional cell carcinoma of the bladder. 17 patients (24%) had unresectable bladder tumour as the sole site of disease; all other patients had metastatic disease. 53% of the patients displayed at least two sites of tumour involvement.

Response to chemotherapy

Among the 67 evaluable patients, 13 patients (19%) achieved CR and 25 patients (38%) had PR for an objective response rate of 57% (95% CI 45–69%). 16 patients had SD and 13 patients progressed while on chemotherapy. Median follow-up of this study currently is 20 months (range 4–51). We studied whether certain pretreatment characteristics of the patients (sex, performance status, prior therapy, sites of disease, number of disease sites per patient) may have influenced the response: only the patients with a good performance status (0, 1) had a significantly higher objective response rate than those with a poor one ($P < 0.02$).

Complete response

The 13 patients who achieved a CR are shown in Table 2. Complete responses (CR) were noted in all tumour sites except in bone. The median duration of response was 15 months (range

Table 1. Patients' characteristics

Patients	
Total	70
Evaluable	67
Median age, years (range)	57 (27–75)
Sex: male/female	63/7
Median WHO performance status	1
Prior therapy	
Cystectomy	27
Systemic chemotherapy	9
Radiation to pelvis	14
Sites of disease	
Bladder (as sole site)	40 (17)
Lymph nodes, abdominal	33
Lung	20
Bone	18
Liver	11
Peripheral node	9
Pelvic mass	7
Other (prostate, eye, skin etc.)	7
Number of disease sites per patient	
One	33
Two	20
Three or more	17

All patients had transitional cell carcinoma of the bladder (as site of origin).

Table 2. Complete response group

Patient no.	Age/sex	Disease sites	Sites of relapse	Freedom from progression* (mo)	Survival (mo)
1	50/M	Bladder, retroperitoneal nodes		—	44+
2†	44/M	Pelvic mass	—	41+	41+
3	62/M	Bladder unresectable	—	34+	34+
4	58/M	Bladder unresectable	Bladder	19	19
5	64/M	Lung, retroperitoneal nodes	Brain	18	18
6	53/M	Retroperitoneal nodes	Liver	18	18
7	46/M	Liver	Liver	17	27+
8	58/M	Peripheral nodes	—	13+	13+
9†	62/M	Pelvic mass retroperitoneal nodes	—	13+	13+
10	61/M	Liver	Peritoneum	7	9
11	58/M	Retroperitoneal nodes	Pelvic mass	6	19
12	65/M	Bladder, peripheral nodes pelvic mass	—	5+	5+
13	50/M	Bladder lung	Lung	3	15

($n=13$).

*Freedom from progression denotes period from onset of treatment to time of disease recurrence.

†Radiotherapy previously given.

No patient had received prior systemic chemotherapy.

3–41+). Median survival was 18.5 months. 3 patients are continuously disease-free at 34, 41, 44 months, respectively, and none of these patients had visceral disease. 7 patients have relapsed, 4 of them in a previously non-involved site; 1 patient suffered an isolated brain relapse; 1 patient who progressed in the same involved site (liver) after a disease-free interval of 1 year obtained a good PR when he was retreated with M-VAC. Median survival of the relapsing patients was only 4 months.

Partial response

The median duration of response of the 25 patients was 16 months (range 4–51+). Of note, 6 of the PRs have not progressed at 20+ months; 2 of these patients had definitive initial bone involvement; they remain well with an abnormal bone scan at 27 and 51 months, respectively. 2 other patients with retroperitoneal lymph node involvement received six cycles of M-VAC followed by local irradiation (45 Gy): they remain with persistent radiological abnormalities in the retroperitoneum at 20+ months. 1 patient with bladder and pelvic nodes involvement achieved a PR with chemotherapy; he developed lung metastases 11 months later which were resected, but has not relapsed almost a year after the thoracotomy.

4 patients achieved a CR after surgical resection of residual disease in the bladder. 2 of these patients are disease-free at 22+ and 27+ months, respectively. 1 patient had an isolated relapse in the brain at 12 months, the other relapsed in the liver at 26 months.

Survival

Median survival of all 70 patients was 13 months; the estimated probability of surviving for 18 and 24 months was 37% (95% CI 12%), and 27% (12%), respectively as shown in Fig. 1.

Of the 54 patients who have had a minimum follow-up of 2 years, 8 patients (15%) are disease-free or have stable residual disease. 4 patients remained alive at 36 months; 3 patients are alive and disease-free at 41, 44, 51 months, respectively. 1 patient died of disease at 50 months.

Not surprisingly, the 33 patients who had visceral metastases had a significantly lower survival ($P < 0.005$), than the 37 patients with nodal and/or bladder involvement.

Delivery of chemotherapy

The 70 patients received 327 cycles of M-VAC chemotherapy (mean 4; range 1–14). Only 131 cycles (40%) were given for both days 15 and 22, with myelosuppression being the major reason that chemotherapy could not be delivered. Only 15 patients (21%) received treatment without delays in drug administration or modifications from the planned M-VAC schedule.

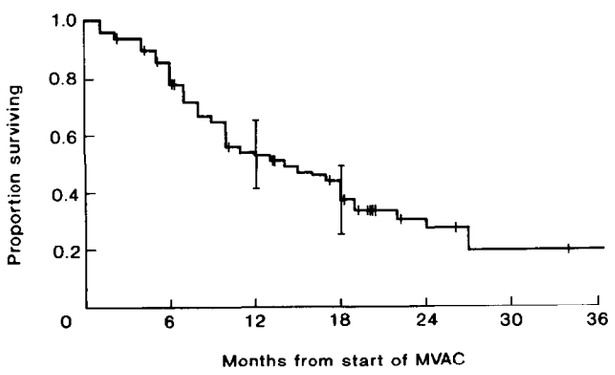

Fig. 1. Survival. | censored patients.

Table 3. Toxicity

	No.	%
Haematological (WHO grade 3 and 4)		
White blood count (10^3 cells/mm^3)		
1.1–2.0	12	17
<1.0	11	16
Platelets (cells/mm^3)		
25 000–49 000	2	3
<25 000	6	9
Mucositis (grade 3 and 4)	6	10
Nausea and vomiting (grade 3 and 4)	7	16
Serum creatinine >2 mg/dl	0	0
Neurotoxicity	2	3
Cardiotoxicity	2	3

The median received dose intensity for the first four cycles of M-VAC was not significantly different among the CR, PR and SD patients being 0.84, 0.77 and 0.75, respectively.

Toxicity

The number of patients who suffered major toxicities (WHO grade 3 or 4) are displayed on Table 3. Granulocytopenia was the dose limiting toxicity. 2 patients experienced a nadir sepsis, but there were no drug-related deaths. No patient developed a serum creatinine above 2 mg/dl. 2 patients experienced a peripheral neuropathy which was not disabling.

Of the 2 patients who suffered cardiotoxicity, 1 patient had an episode of angina during the administration of the chemotherapy, and 1 patient had a decrease of 25% of the left ventricular ejection fraction.

DISCUSSION

Our report which is one of the largest study of M-VAC chemotherapy in advanced carcinoma of the bladder, clearly shows that this combination is active with 1 patient out of 5 achieving a complete response and over 50% of the patients getting on objective response. More important, of the 54 patients who have a minimum follow-up of 2 years, 8 patients (15%) are disease-free or have stable residual disease; some will probably be cured.

Although we did not attempt to evaluate quality of life, we found that the toxicity of the regimen was acceptable and that in particular a good number of patients with PRs only had a better performance status at the completion of M-VAC chemotherapy.

Interestingly, some of the PRs have not progressed more than 3 years after starting treatment—the longest partial responder being at 51+ months—and this is certainly due to the fact that in some cases as with lymphoma or testicular tumours, "residual" disease shown by imaging techniques represents only fibrous tissue.

Our results compare favourably with other investigators. Recently, Sternberg *et al.* from the Memorial Hospital reported on 121 patients with advanced transitional cell carcinoma treated with the M-VAC regimen [9]. They obtained a 72% objective response rate with 25% clinical complete responses. Although our response rate is slightly lower, the median survival is identical, 13 months in both studies, and the estimated probability of 2-year survival similar: 29% (CI 8%) compared with

27% (12%) in our study. The American intergroup trial randomised 121 patients to the M-VAC regimen. There were 23 PR and 15 CR (33% objective response rate), with median survival time of 12.6 months. A Japanese group treated 66 patients with M-VAC [11]. In the 58 evaluable patients there were 23 PR and 10 CR (57% objective response rate). The median survival time was 8 months.

In their small series of 30 patients with advanced transitional cell carcinoma who had measurable disease treated with the same regimen, Tannock *et al.* reported a 40% response rate with only 13% clinical complete responses [12]. Almost all of their patients had distant metastases and the 5 patients with disease confined to the pelvis and lower abdomen had bulky disease. This probably explains the difference in response rate with the Memorial Hospital series.

In 1985, Harker *et al.* reported a 28% CR rate on 50 evaluable patients with metastatic transitional cell carcinoma of the urinary tract treated with cisplatin, methotrexate and vinblastine (CMV) [3]. No doxorubicin was used. Although the median survival was only 8 months, the noticeable CR rate could be partly explained by the fact that the cisplatin dose used (33.3 mg/m^2 per week) was almost twice as high as that used in the M-VAC regimen (17.5 mg/m^2 per week). On the other hand, in 1990, the MD Anderson Cancer Center published a randomised trial comparing the CISCA regimen (cyclophosphamide, doxorubicin, cisplatin) with the M-VAC chemotherapy in patients with metastatic urothelial cancer. Response rate and median survival were significantly higher in the M-VAC-treated patients [13]. In the CISCA regimen, cisplatin was delivered at 100 mg/m^2 every 3–4 weeks instead of 70 mg/m^2 every 4 weeks, as in M-VAC. At this time, we still do not know if there is a dose intensity relationship on response rate with cisplatin.

One problem with the M-VAC regimen is the difficulty to administer methotrexate and vinblastine on days 15 and 22 because of myelosuppression. In our study, only 40% of the cycles were given with both days. Day 15 is very often omitted: in Tannock's report only 15% of the courses were given including this day. One could certainly improve on that with the administration of growth factors. Indeed, Gabrilove *et al.* [14], treated 18 patients with M-VAC and the addition of recombinant human granulocyte colony-stimulating factor (rhG-CSF): all 18 patients were capable of receiving chemotherapy on day 14 of the first cycle, in marked contrast to the second cycle (when chemotherapy was given alone) during which only 5 of 17 evaluable patients (29%) were qualified to receive it on day 14 ($P = 0.0015$).

What have we learned from the various phase II/III trials of chemotherapy for advanced bladder cancer during the 1980s? First, that bladder cancer is a chemosensitive tumour. Second, that combination chemotherapy is superior to single-agent, as reported recently by Loehrer *et al.* [10], and that among the different combinations, the M-VAC regimen is presently one of the most effective [13]. Third, that a significant proportion of patients attain a complete response with some being long-term survivors. Presently, most of the oncologists looking after patients with metastatic bladder cancer and with a good performance status [15] would find it unethical not to recommend a trial of combination chemotherapy.

Clearly, some progress has been made, but the most pressing question remains: how could we improve on the complete response rate which is the prerequisite for cure and at the same time decrease toxicity? Use of M-VAC and G-CSF has been shown to permit increased drug delivery and to decrease toxicity [14]. Recent data from MD Anderson suggest that escalated doses of M-VAC with granulocyte-macrophage colony-stimulating factor (GM-CSF) may translate into an improved therapeutic outcome [16]. A better understanding of drug resistance may allow us to reverse the expression of *mdr* gene which is involved in the resistance of the two agents doxorubicin and vinblastine [17]. We also need to develop new and better agents.

The efficacy of combination chemotherapy in the metastatic setting has prompted investigators to use chemotherapy in the adjuvant or neoadjuvant setting to try to eradicate micrometastases.

Currenty, two large-scale randomised studies are in progress assessing the impact of chemotherapy on survival; one from the MRC–EORTC evaluating the benefit of three cycles of neoadjuvant CMV before definitive local therapy; the second from the Intergroup comparing three cycles of M-VAC administered before cystectomy with cystectomy alone. We are awaiting the results of these two studies with great interest, and hope that the benefit will be of the same magnitude as with the one obtained with some of the solid tumours such as breast cancer.

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Left Handedness is Uncommon in Breast Cancer Patients

H. Olsson and C. Ingvar

Left handedness was found to be significantly less common among patients with breast cancer in southern Sweden (1.5%) than among a female referent population (5%) ($P<0.0025$). The findings lend support to theories suggesting that hormonal factors in early life are of importance both for handedness and for the risk of breast cancer.
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INTRODUCTION

THEORIES ON breast cancer have focused on the importance of events in the early reproductive years [1–9]. Trichopoulos has suggested that events in the prenatal and perinatal years could have an important bearing on breast cancer carcinogenesis [10]. Often only retrospective studies about factors for cancer development in these early periods are possible, since prospective studies would take generations.

Cerebral dominance of the left or right hemisphere, expressed as right or left handedness, could be partly dependent on the hormonal perinatal and prenatal environment [11–13]. Thus a higher rate of left handedness in the offspring could be caused by a more pronounced testosterone exposure to the fetus either by the mother or the fetus itself [11–13]. If a hormone exposure in early years would later have a bearing on the risk of developing breast cancer, an increased androgen exposure to the female fetus would reduce the risk of developing breast cancer. On the other hand, an increased oestrogen exposure instead would augment the risk [10].

In the present investigation, the frequency of left-handedness has therefore been investigated in a large group of breast cancer patients and female referents from the general Swedish population.

PATIENTS AND METHODS

Consecutive breast cancer patients (n = 395) at the Department of Oncology, University Hospital, Lund, were interviewed through a standardised structured questionnaire about handedness at their primary visit for postoperative radiation treatment. The median age of the patients was 62 (range 28–90) years. The department serves as the radiation treatment centre for the Southern Health Care Region in Sweden and has a catchment area of 1.2 million inhabitants. The recruitment is population-based. Except for ongoing randomised trials excluding approximately one third of postmenopausal women and one fifth of premenopausal women from radiation, the overall majority of breast cancer patients are seen. 5158 women interviewed through health care investigations from Swedish centres for Occupational Health in 1983–1984 was used as referents [14]. These women were occupationally active and their age ranged from 15–65 (median 41) years. Left handedness was defined as preferentially using the left hand when writing as an adult. Women using both hands equally were classified as right handed.

The Poisson distribution was used to compare the two groups.

RESULTS

Of the breast cancer patients, 6/395 (1.5%) were left handed compared with 258/5158 (5%) of the referents. This difference was highly significant ($P<0.00025$). 4 out of 6 (67%) left handed women with breast cancer also had a left sided breast cancer in comparison with 211/389 (54%) right handed women (OR = 1.7, 95% CI 0.3–12.7).

DISCUSSION

The present investigation shows that left handedness is less common among patients with breast cancer than among the general population. Theories have related prenatal and perinatal androgen exposure from the mother to the fetus as a possible cause for left handedness [11–13]. Our findings indicate that an increased exposure to testosterone in early life permanently reduces the risk of breast cancer for a woman and thus support theories on the age dependency of breast cancer carcinogenesis.

There are problems in determining handedness. First, there are individuals who are ambidextrous. By only classifying women preferentially writing with the left hand as left handed we hoped to avoid the possibility of a classification bias. Second, handedness was determined in adults and this is preferable since very young children may have a not fully developed cerebral

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