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# COMBINATION CHEMOTHERAPY IN ADVANCED POSTMENOPAUSAL MAMMARY CARCINOMA

## A comparison between VAC and VACM therapy

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Combination chemotherapy yields an objective response of 60 per cent (40–80 %) in patients with advanced postmenopausal breast malignancy (CARBONE et coll. 1977, TORMEY & NEIFELD 1977). In randomized trials combination chemotherapy has proved a higher efficacy than single alkylating agents (CANELLOS et coll. 1976, MOURIDSEN et coll. 1977). However, Adriamycin as a single drug has had the same response rate as combination chemotherapy (HOOGSTRATEN et coll. 1976, CARBONE et coll., NEMOTO et coll. 1978) and must be considered the most effective single drug.

Adriamycin regimens have shown the same or higher efficacy than regimens not containing Adriamycin (BLUMENSCHEIN et coll. 1974, DE LENA et coll. 1975, BROWN & WARD 1976, TORMEY & NEIFELD, TORMEY et coll. 1977).

The optimum number of drugs in an Adriamycin regimen is unknown. In a recent review the collected data of response rates of different regimens found a levelling off at 3 to 4 drug regimens (TORMEY & NEIFELD). At this department a regimen of 4 drugs consisting of Vincristine, Adriamycin, Cyclophosphamide and Methotrexate with citrovorum factor rescue (VACM regimen) produced an overall response rate of 78 per cent in a phase II investigation (MATTSSON et coll. 1977). It was built up on the basis of synergism between Adriamycin and Cyclophosphamide (CORBETT et coll. 1975, JONES et coll. 1975) and Adriamycin overcoming resistance to Methotrexate (HILL et coll. 1976). Vincristine was included as an overlapping toxicity did not exist

Submitted for publication 17 January 1979.

and as good results already have been achieved with Adriamycin–Vincristine therapy (DE LENA et coll.). The complicated and time-consuming procedure of Methotrexate with citrovorum factor rescue (M-CFR) limited the wider use of VACM regimen. Furthermore, the cost of M-CFR is high. Therefore a randomized investigation was initiated comparing Vincristine–Adriamycin–Cyclophosphamide (VAC) with or without M-CFR (VACM).

## Material and Methods

All patients with metastatic mammary carcinoma in Malmö, a city of about 250 000 inhabitants, are treated in this department. Between May 1976 and May 1978 65 patients have been included in this randomized trial as they fulfilled the following eligibility criteria: (1) Postmenopausal (either natural or artificial) advanced breast malignancy in patients less than 71 years old. Postmenopausal disease is defined as at least 12 months spontaneous menostasia or at least 12 months after castration, (2) measurable or non-measurable but evaluable lesions, and (3) Karnofsky's performance index $\geqslant 50$ points.

Patients who relapsed or progressed during hormonal treatment were included, when the additive endocrine treatment had been discontinued for one month and no withdrawal effect could be observed.

Previous chemotherapy was allowed except treatment with Adriamycin alone or in combination with other drugs. One patient still alive after 3 months and randomized to VAC therapy was not evaluable, as the treatment was discontinued after 2 courses because of progressing brain metastases. No patient was lost to follow-up. Seventeen patients have died and all were autopsied.

The patients were randomized to either VAC regimen—combination chemotherapy with Vincristine (1 mg i.v. day 1), Adriamycin (50 mg/m$^2$ body surface i.v. day 1), Cyclophosphamide (100 mg/m$^2$ body surface orally days 1–8)—or VACM regimen—VAC plus Methotrexate with citrovorum factor rescue (M-CFR; M 200 mg on day 8 by drip infusion during 3 h with subsequent CFR 15 mg 3 times orally administered at 6, 12 and 18 h after the end of M-infusion).

The interval between the first day of treatment and start of next course was 21 days for 6 courses. Thereafter the courses were repeated every 4th week (a new course starts on day 28) until a total dose of Adriamycin 500 mg/m$^2$ body surface. Then, Adriamycin was replaced by 5-Fluoro-Uracil (F; 750 mg/m$^2$ body surface i.v. on day 1). The treatment was continued with the other drugs as before and the courses were repeated every 6th week (next course starts on day 42) until a relapse or 2 years of complete remission. Vincristine was given until neurotoxicity of clinical importance was observed, which is defined as a decreased muscular strength, recurrent severe constipation or paresthesia, which interfered with the daily living of the patients. Thus, the patients randomized to VAC and VACM, respectively, received continuous treatment with VFC and VFCM.

A fixed dose reduction scheme was used according to the pre-treatment values of

**Table 1**

*Dose modification scale**

| Leukocytes* ($\times 10^9$/l) | Platelets* ($\times 10^9$/l) | Per cent of calculated dose of | | | |
|---|---|---|---|---|---|
| | | Vincristine | Adriamycin | Cyclophosphamide | Methotrexate |
| 3.9 – 3.0 | 125 – 100 | 100 | 75 | 75 | 100 |
| 3.9 – 2.0 | 99 – 75 | 100 | 50 | 50 | 75 |
| ≤ 1.9 | ≤ 74 | | prolongation of interval | | |
| | BSF (per cent) | | | | |
| | 9 | — | 100 | — | — |
| | 10–15 | — | 75 | — | — |
| | 16–25 | — | 50 | — | — |
| | ≥ 26 | — | 25 | — | — |

* Pre-treatment values.

leukocytes and platelet counts (Table 1). The dose of Adriamycin was adjusted to the liver function as measured by bromsulphalein retention (BSF; Table 1). If an initial pathologic BSF was found, the analysis of BSF was repeated every 3rd to 4th cycle or until a normalization was observed.

All patients received at least 4 courses. If a progressive disease was then observed in patients with soft tissue or visceral metastases, the therapy was discontinued. Independently of the results of skeletal radiography the patients with skeletal metastases received at least 10 courses if a subjective improvement as measured by Karnofsky's performance index was observed and if no progression of other metastases or a new lesion was detected. Otherwise, the patients continued treatment until a progressive disease or a relapse occurred.

The base line examinations included; physical and gynecologic examination, assessment of Karnofsky's performance index, photography of skin metastases, radiography of chest, skull, axial skeleton and pelvis, mammary radiography of palpable breast lesions, fine needle aspiration biopsy of accessible and clinically equivocal lesions in the soft tissue, breast, lymph nodes, lungs and liver, scintigraphy of the skeleton ($^{99}Tc^m$ or $^{85}Sr$) and of the liver. Laboratory examinations included determination of haemoglobin, erythrocytes, leukocytes, platelets, reticulocytes, differential cell counts, electrolytic status (Na/s, K/s, Ca/s), creatinine/s, urate/s, liver tests (BSF, ASAT, ALAT, Bil, ALP, GT, LD), carcinoembryonic antigen (CEA) and protein analysis. Detailed results of these examinations will be presented elsewhere (MATTSSON et coll., in preparation).

A dominant metastatic site in soft tissue was revealed in 2 patients, in skeleton in 18 and in viscera in 44 (Table 2). The number of metastatic organs involved was 1 to 6 for both VAC regimen (median 2 organs) and VACM regimen (median 3 organs; Table 3).

**Table 2**

*Clinical characteristics—VAC versus VACM*

| | VAC<br>No. of patients | VACM<br>No. of patients |
|---|---|---|
| Entered | 32 | 33 |
| Evaluable | 31 | 33 |
| Previous therapy of metastases | | |
| Hormonal therapy | 19 | 17 |
| Radiation therapy | 12 | 16 |
| Chemotherapy | 1 | 2 |
| Dominant site of metastases | | |
| Soft tissue | 2 | — |
| Skeleton | 9 | 9 |
| Viscera | 20 | 24 |
| Age | | |
| Median | 63 years | 61 years |
| Range | 48–69 years | 32–70 years |
| Free interval | | |
| Medial | 16 months | 26 months |
| Range | 0–142 months | 0–140 months |
| Karnofsky index | | |
| Median | 70 points | 70 points |
| Range | 50–90 points | 50–90 points |

**Table 3**

*Complete (CR) plus partial (PR) responses related to sites of metastases*

| Metastatic sites | No. of patients/No. of CR + PR | | | |
|---|---|---|---|---|
| | VAC | Per cent | VACM | Per cent |
| Skin | 6/9 | (66) | 8/10 | (80) |
| Lymph nodes | 9/11 | (82) | 12/18 | (67) |
| Breast | 1/1 | — | 3/3 | — |
| Lung | 9/12 | (75) | 10/14 | (71) |
| Pleura | 5/5 | — | 5/8 | — |
| Liver | 3/5 | — | 6/8 | — |
| Ovary | 2/3 | — | 1/5 | — |
| Mediastinum | 0/3 | — | 1/2 | — |
| Other sites | 2/13 | (15) | 5/8 | — |
| Skeleton | 12/18 | (67) | 15/22 | (68) |

**Table 4**

*Results ≥ VAC versus VACM regimens*

| | VAC regimen | | | Alive in remission | VACM regimen | | | Alive in remission |
|---|---|---|---|---|---|---|---|---|
| | No. of patients | Duration of remission | | | No. of patients | Duration of remission | | |
| | | Median | Range | | | Median | Range | |
| Complete remission | 7 | 18+ | (12+–25+) | 5 | 9 | 13+ | (2+–27+) | 8 |
| Partial remission | 14 (68 %) | 7 | (2–18+) | 8 | 16 (76 %) | 11+ | (3+–22+) | 9 |
| No change | 8 | 4+ | (4–12+) | 3 | 5 | 5 | (3+–8) | 1 |
| Progressive disease | 2 | — | — | — | 3 | — | — | — |

No difference existed between the 2 treatment groups with respect to age, free interval, previous therapy of metastases or pre-treatment Karnofsky's performance index (Table 2).

The results were assessed from physical examinations and assessment of Karnofsky's performance index before every course. In all patients radiography of the lung and of the skeleton as well as scintigraphy of the liver and the skeleton were performed at intervals of 3 months or less. All metastatic lesions in the lung, skeleton, liver and soft tissues were examined with radiography, scintigraphy or photography before every 3rd course up to 12 courses. Determinations of haemoglobin, leukocytes and platelets were made every week for 12 courses. Thereafter, depending upon previously clinical outcome, but at least once in free interval of therapy and on the day of starting a new course. Before at least every 3rd course the laboratory examinations included electrolytic status, creatinine and liver tests. CEA and protein analysis were examined every 3rd to 4th months.

The criteria used for remissions were those recommended by HAYWARD et coll. (1977); complete remission is the disappearance of all known disease. Lytic bone metastases must have calcified at radiography. Partial remission is a $\geqslant 50$ per cent decrease in measurable lesions and objective improvement in evaluable but non-measurable lesions. New lesion must be excluded. No change is recorded when the lesions are unchanged ($<50\,\%$ decrease or $<25\,\%$ increase in the size of measurable lesions). No new lesion is accepted. Progressive disease is recorded when a new lesion appears, some lesion progresses or when some lesion regresses when other progresses. The duration of remission and of the survival was calculated from the date the treatment began.

## Results

The overall response rate to VAC regimen and VACM regimen was 68 and 76 per cent, respectively (Table 4). Up to October 1978 no significant differences was

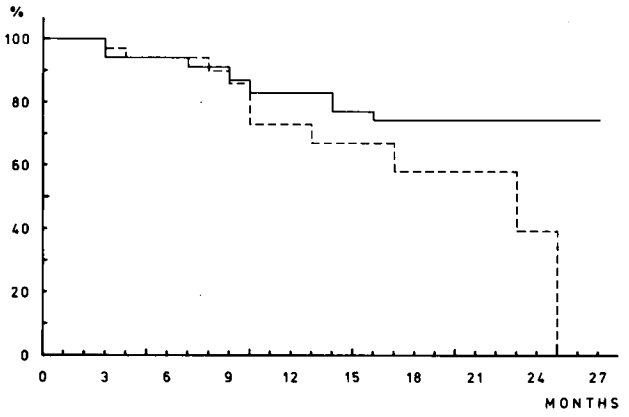


Fig. 1. Survivals in patients treated with VAC (---) and VACM (——) regimen.

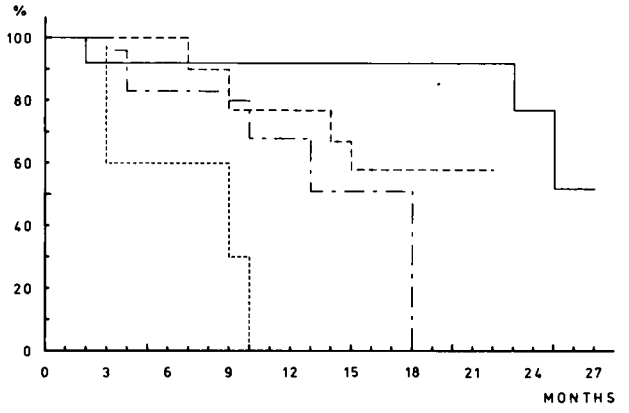


Fig. 2. Survivals in relation to remission in patients treated with VAC or VACM regimen. —— Complete remission. --- Partial remission. -·- No change. ···· Progressive disease.

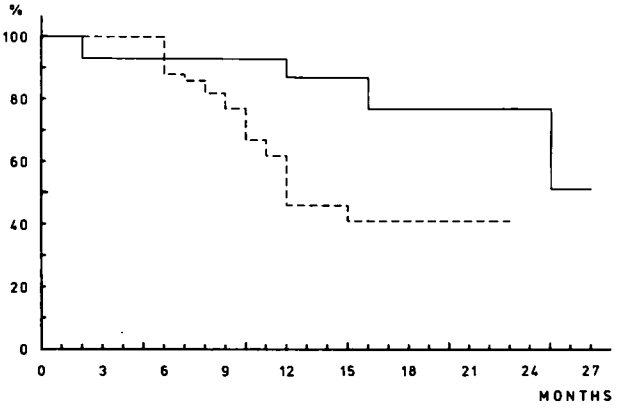


Fig. 3. Duration of remission in patients treated with VAC or VACM regimen. —— Complete remission. --- Partial remission.

**Table 5**

*Results in relation to dominant site of metastases (per cent in parentheses)*

| | Objective response | |
|---|---|---|
| | VAC | VACM |
| Soft tissue | 2/2 | — |
| Skeleton | 6/9 (66) | 8/9 (88) |
| Viscera | 13/20 (65) | 17/24 (71) |
| Total | 21/31 (68) | 25/33 (76) |

No significant relation to dominant site of metastases ($0.1 < p < 0.2$, Kruskal–Wallis 1-way analysis of variance by ranks).

noted in the length of remissions ($p = 0.7$, log rank test), in the survival of responders ($0.1 < p < 0.25$, log rank test) or survival of the total group of patients ($0.25 < p < 0.5$, log rank test; Fig. 1) between the two regimens. The patients who obtained a remission by VAC or VACM regimen survived significantly longer than non-responders (unchanged or progressive disease; $0.001 < p < 0.01$, log rank test; Fig. 2). Complete responders had a significantly longer duration of remission than partial responders ($0.025 < p < 0.05$, log rank test; Fig. 3).

The median durations of remissions have not been reached at 18+ months and 13+ months for patients obtaining a complete remission by VAC therapy and VACM therapy, respectively (Table 4). Each one patient with a complete remission by VAC and VACM regimen died in intercurrent diseases. The patient in the VAC group developed an acute myeloblastic leukaemia after 25 months of therapy and died within a few days after diagnosis. The patient in the VACM group succumbed in a traffic accident. Autopsies could not reveal either macroscopically or microscopically any remaining malignant tissue in the breast, in the original sites of metastases or in other organs. Thus, only one of 16 complete responders have had a recurrence.

Six of 14 patients with partial remission treated with VAC regimen have relapsed after 2 to 9 months (median 6 months) compared with 7 of 16 patients with partial remission induced by VACM regimen, where the relapses were observed after 10 to 15 months (median 12 months). The recurrent tumor sites were in previous regressing lesions in 5 patients, in a new site in 5 patients (4 brain, 1 liver) and combined relapses in 3 patients. Five of the 6 patients relapsing during VAC therapy and 2 of the 7 patients relapsing during VACM therapy have died. At autopsy 4 of these patients had predominant cerebral metastases and only insignificant spread in other organs (lung, pleura, liver, skeleton, soft tissues), which were the dominant sites before

**Table 6**

*Results in relation to the number of metastatic organs (per cent in parentheses)*

| No. of organ sites | Objective response | |
|---|---|---|
| | VAC | VACM |
| 1–2 | 14/19 (74) | 11/12 (92) |
| ⩾3 | 7/12 (58) | 14/21 (66) |

Significant relations to the number of organ sites of metastases ($p < 0.001$, Kruskal–Wallis 1-way analysis of variance by ranks).

combination chemotherapy. The deaths were caused by the cerebral metastases. The remaining 3 patients had wide spread metastases.

The response rate in different metastatic sites appears in Table 3. The objective response in skeleton as measured by skeletal radiography was 67 per cent in the VAC group and 68 per cent in the VACM group. The number of courses required to obtain a measurable objective response was 3 to 11 courses (median 7 courses). No difference was found in response rate in relation to site of metastases except in mediastinum, ovary, and other sites as brain, peritoneum, omentum, bowel and uterus.

The response rate and the duration of remissions in relation to dominant site of metastases did not differ significantly ($0.1 < p < 0.2$, Kruskal–Wallis 1-way analysis of variance by ranks; Table 5).

A significant correlation to an objective response and the number of metastatic organ sites was observed ($p < 0.001$, Kruskal–Wallis 1-way analysis of variance by ranks; Table 6).

When measured before starting a new course the Karnofsky performance index improved with 0 to 30 points (median 20 points) and 0 to 40 points (median 20 points) in responders to VAC therapy and to VACM therapy, respectively. Furthermore, 8 of 13 patients with unchanged disease had an improvement with 10 to 30 points (median 20 points).

The toxicity of both regimens was acceptable. The nadir values of leukocytes and platelet counts were evaluable in 312 courses of VAC regimen and 360 courses of VACM regimen (Table 7). Nadir values of leukocytes below $2.0 \times 10^9$/l were observed in 14 and 19 per cent of the courses of VAC and VACM, respectively. Three patients had a bronchopneumonia, which resolved by appropriate antibiotic therapy. Otherwise no infections related to the chemotherapy were registered. Less than 5 per cent of the courses were followed by platelet counts below $74 \times 10^9$/l. No secondary bleedings occurred. No renal (as measured by S-creatinine, electrolytic status) or liver (liver tests) toxicity were recorded.

**Table 7**

*Toxity*

| Nadir values | VACM | | VAC | |
|---|---|---|---|---|
| | No. of courses | Per cent | No. of courses | Per cent |
| Leukocytes | | | | |
| $3.9-3.0\times10^9$/l | 75/360 | 21 | 79/312 | 25 |
| $2.9-2.0\times10^9$/l | 124/360 | 34 | 98/312 | 31 |
| $\leqslant 1.9\times10^9$/l | 67/360 | 19 | 45/312 | 14 |
| Platelets | | | | |
| $124-100\times10^9$/l | 24/360 | 7 | 35/312 | 11 |
| $99-75\times10^9$/l | 28/360 | 8 | 16/312 | 5 |
| $\leqslant 74\times10^9$/l | 11/360 | 3 | 14/312 | 4 |

The VACM regimen was discontinued in 3 patients when still in remission. The reasons were reversible cardiotoxicity (supraventricular arrythmia) in one patient (at a total dose of 420 mg Adriamycin/$m^2$ body surface), no available vessel for injection of drugs in one patient and cystitis together with severe myelosuppression in one patient, who had bone marrow involvement confirmed on biopsy and extensive previous irradiation.

Nausea of varying severity occurred in 28 patients (85%) treated with VACM regimen and in 24 patients (77%) treated with VAC regimen. Because of severe nausea 2 patients treated with VAC regimen discontinued the treatment after 10 and 12 courses, respectively. In these patients Adriamycin was replaced by 5-Fluoro-Uracil. Otherwise the treatment was continued as planned. They are still in remission and have now acceptable tolerance for the chemotherapy.

All patients had reversible alopecia. On 5 occasions 3 patients in the VACM group had transient, moderate mucositis.

No severe neurotoxicity was observed. In 8 (13%) patients (4 VAC, 4 VACM) Vincristine was discontinued at 4 to 16 mg (median 12 mg) because of paresthesia without paresis, which was always reversible.

## Discussion

The groups of patients balanced well according to age, previous therapy of metastases, dominant site of metastases and pre-treatment Karnofsky's performance index. However, there might be more patients with a worser prognosis in the VACM group as the median number of metastatic organ sites in this group was 3 compared to 2 in the VAC group (MATTSSON et coll. 1977).

In this previous report no significant difference was found between the patients

receiving VAC or VACM therapy in relation to response rates, duration of remissions, survivals and side effects. Thus, M-CFR treatment on day 8 might be discontinued. This will decrease the total cost of the drugs with 30 per cent or about 875 dollars for an average patient. Furthermore, as each visit in the department for having chemotherapy costs about 100 dollars, treatment with VAC only will save further 1 100 dollars in an average patient. Based on these data it was decided to omit M-CFR. However, some caution in the evaluation of the results must be observed, as there might be more patients in the VACM group with a worser prognosis (median number of metastatic sites 3). The actuarial survival curve points to a longer survival in the VACM group. Anyhow, both regimens give results, which favourably can be compared to other regimens on records (BLUMENSCHEIN et coll., DE LENA et coll., BROWN & WARD, CANELLOS et coll., HOOGSTRATEN et coll., CARBONE et coll., LOKICH et coll. 1977, TORMEY & NEIFELD, RUSSEL et coll. 1978).

The median duration of the remissions has not yet been reached. By actuarial analysis they are projected to be 12 months for partial remission and more than 27 months for complete remission and thus longer than usually reported (CARBONE et coll., TORMEY & NEIFELD). One reason for the length of remission in the present series might be the long-standing treatment and the regimen used as continuous therapy (VAC and VACM followed by VFC and VFCM, respectively).

It is important to continue the therapy in responders for a long time as the cytotoxic drugs have an effect, which follows first order kinetics (SKIPPER 1971, SCHABEL JR 1977). When the maximum dose of Adriamycin is reached, the continuous therapy in some series is either absent (SMALLEY et coll. 1977, NEMOTO et coll.) or single drug therapy (TORMEY et coll.), which must be considered too weak to be able to prolong the duration of remissions. The present patients were treated as long as a no change was observed or for at least 2 years after a complete remission. Thus, the median duration of patients with unchanged disease is slightly inferior to unmaintained median remission for responders (CANELLOS et coll., SMALLEY et coll.).

In several reports on Adriamycin regimens the continuous therapy in CMF-(P) regimen; DE LENA et coll., KENNEALEY et coll. 1978, RUSSEL et coll.). This standard regimen has disadvantages from a theoretic point of view, as a negative interaction by an inhibition of the metabolic transfers of the drugs at the level of thymelate synthetase might be obtained. In line with these considerations BERTINO (1976) has found in animal experiments, that 5-Fluoro-Uracil given before Methotrexate caused an antagonism and when 5-Fluoro-Uracil and Methotrexate were administered at the same time, which is the general clinical practice, no additive effect was observed. On the other hand, a synergy was found, if Methotrexate was administered 1 to 4 hours before 5-Fluoro-Uracil. In the present series an interval of one week did exist, when both 5-Fluoro-Uracil and Methotrexate were used.

It is not known if and when therapy in long term responders can be discontinued. Considerations require the initial tumor load, the subjective tolerance of treatment, the optimum goal of cure and the risk of secondary malignancy. An increased rate

of secondary malignancies exists in patients receiving continuous chemotherapy for a long time (EINHORN 1978, PENN 1978). However, in a recent report weekly adjuvant Thio-Tepa therapy for one year in patients operated upon for breast malignancy did not increase the frequency of secondary tumors 5 to 14 years after the treatment (KARDINAL & DONEGAN 1978). In the present series one patient had a myeloblastic leukaemia, which must be considered as drug induced malignancy. There appears to be no similar report on advanced breast carcinoma, which probably is due to the few long term survivers.

In a recent review MATHÉ (1978) has summarized the importance of the immune status in the patients receiving combination chemotherapy. In a subset of 20 patients in the present series, in accordance with the data of MATHÉ, a normal PHA reactivity was found in the lymphocytes from the responders but a depressed PHA reactivity in the lymphocytes from the non-responders. On the other hand, the mitogenic reactivity of B-lymphocytes when stimulated by the Cowan I-strain of staphylococcus aureus was depressed in the responders (BANCK et coll. 1979). Blocking antibodies are supposed to be an important factor in the clinical course of malignant diseases (HELLSTRÖM et coll. 1971). The depression of B-lymphocyte mitogenic reactivity in vitro in the responders might have caused an 'un-blocking' effect, which produced an augmentation of the immune function in the patients resulting in an increased efficacy of the chemotherapy. Thus, these findings of immune status may have contributed to the long duration of remission.

The effect of VAC and VACM therapy in osseous metastases was better than with other regimens (CANELLOS et coll., TORMEY & NEIFELD, RUSSEL et coll.) but the same as previously reported by MATTSSON et coll. (1977). The present results might be due to the long-standing therapy. The patients with osseous metastases and subjective improvement continued treatment until 10 courses, independent of the results of skeletal surveys. As measured by skeletal films, about two thirds of the patients in the present and the previous reported series had an objective response, but several courses (median 7 courses) are required before an objective effect can be demonstrated.

The results of VAC and VACM therapy were not influenced by the individual sites of metastases, besides metastases in the brain, the mediastinum, the uterus and the omentum. This is in contrast to the effect of endocrine therapy, where visceral metastases, particularly metastases in the liver, show regression in a lower frequency than metastases in soft tissue and in the skeleton. Several reports on combination chemotherapy have shown a correlation between the response rate and dominant site of metastases. Thus, the best effect is obtained in soft tissue and the lowest effect in skeletal metastases (CANELLOS et coll., TORMEY & NEIFELD). In the present series no relation between the effect of therapy and dominant site of metastases was found. On the other hand, a strong correlation between the response rate and number of metastatic organs was observed, which indicates that this parameter might reflect the tumor load better than the dominant site of metastases.

An increase of cerebral metastases in patients treated with chemotherapy has been reported (TRANUM & HOOGSTRATEN 1977). In the present series 4 patients had metastases only in the brain. However, the present data do not warrant the use of prophylactic cerebral irradiation. Recently, a retrospective analysis of relapses in 111 complete responders to chemo-immuno therapy showed a recurrence rate of 53 per cent in initial sites of involvement and 30 per cent in new sites. The brain was the site of relapse in 17 patients (25%; LEGHA et coll. 1978). The relapses in the present series correspond roughly to these findings. As proposed by LEGHA et coll., the possibility to maintain the remission by addition of local therapeutic measures must be explored.

The objective toxicity of both VAC and VACM regimen was low. Both regimens were safe in respect to myelosuppression. The low rate of platelet depressions is noticeable. Mucositis occurred seldom. This serious side effect was less common than usually reported for CMF regimen (DE LENA et coll., CANELLOS et coll.). The low rate of objective side effects might be due to that no patient had any impaired renal function and that the dose of Adriamycin was adjusted to liver function as measured by BSF.

The most frequent and troublesome side effect was the high rate of nausea during the first day of treatment, although 12 patients did not experience any nausea. A good relief of the nausea was obtained with 20 mg Metochlopramid intravenously, given a quarter of an hour before the start of the cytotoxic treatment. However, in the free intervals almost all responders had an increased performance status and could lead an ordinary life.

## SUMMARY

A randomized trial comparing Vincristine, Adriamycin, Cyclophosphamide (VAC) with or without Methotrexate with citrovorum factor rescue (VACM) was performed in 64 patients with metastatic postmenopausal mammary carcinoma. Previous treatment of metastases, dominant site of metastases and performance condition were similar in the patients. No significant difference was found in the response rates (complete remission + partial remission; VAC 21/31, VACM 25/33), in the duration of the remissions or in the survivals. The duration of remission in CR was significantly longer than in PR. No serious side effects were observed. The VAC regimen is preferable, particularly with respect to the costs and the simple procedure of administration.

## ZUSAMMENFASSUNG

Ein randomisierter Versuch umfasste den Vergleich von Vincristin, Adriamycin, Cyclophosphamid (VAC) mit oder ohne Methrotrexat mit Citrovorum Factor Rescue (VACM) bei 64 Patienten mit metastatischen postmenopausalen Mammakarzinom. Die Vorbehandlung der Metastasen, die wesentlichen Lokalisationen der Metastasen und die Bedingungen der Durchführung waren bei diesen Patienten gleich. Keine signifikanten Unterschiede wurden in den Responsraten (komplette Remissionen + partielle Remissionen (VAC 21/31, VACM 25/33), Dauer der Remissionen oder dem Überleben) gefunden. Die Dauer der

Remissionen bei kompletter Remission war signifikant länger als bei partieller Remission. Keine ernsthaften Nebeneffekte wurden beobachtet. Das VAC Regim ist vorzuziehen, besonders hinsichtlich der Kosten und der einfachen Administration.

## RÉSUMÉ

Un essai randomisé comparant la Vincristine, l'Adriamycine, le Cyclophosphamide (VAC) avec ou sans Methotrexate avec le citrovorum factor rescue (VACM) a été effectué chez 64 malades atteints de carcinome mammaire métastatique post-ménopausique. Les traitements antérieurs des métastases et le siège principal des métastases étaient semblables chez ces malades. Les auteurs n'ont pas observé de différence significative dans les taux de réponse rémission complète + rémission partielle; VAC 21/31, VACM 25/33), dans la durée des rémissions ou dans les survies. La durée de la rémission avec rémission complète a été significativement plus longue qu'en rémission partielle. Les auteurs n'ont pas observé d'effet secondaire grave; le traitement par VAC est préférable en particulier en raison de son coût et de la simplicité du mode d'administration.

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