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Weekly Adriamycin Versus VAC in Advanced Breast Cancer. A Randomized Trial

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Abstract—*In a prospective randomised study* 128 *patients with advanced breast cancer were treated either with Adriamycin* (20 mg/week) *or vincristine, Adriamycin and cyclophosphamide* (VAC). *An objective response was obtained in* 31 *and* 35% *of patients in the two groups. There was no significant difference with regard to duration of response or survival. Weekly low dose Adriamycin was well tolerated. When subjective side effects occurred, they were usually slight and transient. In approx.* 40% *of the patients no side-effects at all were observed. Eight per cent had alopecia requiring a wig. Only slight myelosuppression could be seen in a few patients and this had no practical implications. Most or all of VAC patients experienced severe toxicity with regard to nausea, vomiting and alopecia. Also myelosuppression was more pronounced among VAC patients. It is concluded that weekly doses of Adriamycin as single agent therapy for advanced breast cancer is as effective as the VAC combination delivered every third week, with considerably less toxicity.*

INTRODUCTION

ADRIAMYCIN is one of the most effective chemotherapeutic agents in advanced breast cancer. Usually it is given in combination with other drugs, i.e. vincristine, cyclophosphamide and 5–fluorouracil (VAC or FAC) every 3 weeks. In a previous prospective study at The Norwegian Radium Hospital the response rate to VAC was 35% [1]. Besides alopecia and bone marrow depression, most patients experienced severe nausea and vomiting.

Non-randomized studies have indicated that weekly low dose Adriamycin as single agent therapy could be comparatively effective with regard to response rate, and without serious toxicity [2] in advanced breast cancer. In a pilot study (unpublished data) undertaken at The Norwegian Radium Hospital, 9 out of 24 pretreated patients responded.

With this background it was felt justified to initiate a prospective randomized study between weekly Adriamycin (Awkly) and VAC in advanced breast cancer.

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PATIENTS AND METHODS

From June 1982 until December 1983 a total of 128 patients with advanced breast cancer were entered into the study. A pretreatment initial white cell count (WCC) of $\geq 4 \times 10^9$/l and platelet (plt) count of $\geq 125 \times 10^9$/l were required. Patients with another type of neoplasm, or other medical conditions which could preclude adherence to the treatment or assessment schedule, were excluded. Metastases were measurable or evaluable. Patients with brain metastases, leptomeningeal affection or osteoblastic lesions as the only manifestation of the disease were excluded. Furthermore patients previously treated with Adriamycin did not enter the study.

All patients had previously received hormone treatment and were considered hormone resistant.

Prior to initial treatment all patients underwent physical examination. Blood count, chest X-ray, bone isotope scan and/or bone survey radiographs and measurements of indicator lesions were obtained in all patients. If indicated by liver function tests, liver scan, ultrasound sonography or computertomography was performed. Brain scans and/or computertomography was performed in those patients who had symptoms or signs suggestive of central nervous system metastases.

Patients were allocated by random numbers to

either Adriamycin 20 mg/week (Awkly) or vincristine 2 mg, Adriamycin 50 mg/m^2 and cyclophosphamide 600 mg/m^2 (VAC) every 3 weeks (Table 1). There was no stratification.

Blood counts were performed before each course of chemotherapy, both for Awkly and VAC. Nadir values betwen VAC courses were not determined. When WCC and/or plt counts before start of a new course were between 3.9–3.0 × 10^9/l and 124–100 × 10^9/l respectively, doses of cyclophosphamide and Adriamycin were reduced by 25% and for the corresponding values 2.9–2.0 × 10^9/l and 99–75 × 10^9/l dose reduction was 50%. For lower values treatment was postponed for 1 week.

The stipulated maximal cumulative dose of Adriamycin in the Awkly regime was 750mg/m^2, and in the VAC regime 500 mg/m^2 (Table 1). Responding patients were treated until the stipulated maximal cumulated dose of Adriamycin and then received maintenance therapy with methotrexate 50 mg and cyclophosphamide 600 mg/m^2 every 4 weeks for a total duration of chemotherapy of 2 yr. Patients who did not respond (progressive disease or no change after 3 months of treatment) received a combination of 5–fluorouracil 1000 mg/m^2 day 1 and 2 and Mitomycin–C 6 mg/m^2 day 2 every 3 weeks (FuMi).

Main patient characteristics are summarized in Tables 3 and 4. There were no significant differences between the two groups with regard to important prognostic factors except that more Awkly patients had received adjuvant chemotherapy than VAC patients (17/62 vs. 8/66, $P = 0.05$). Although significant this must have occurred by chance and didn't favour Awkly patients.

The criteria used for remission were those recommended by WHO [3].

The duration of PR was calculated from start of treatment until progression, while CR was calculated from the time CR could be documented.

STATISTICAL METHODS

The comparability of the two treatment groups with respect to baseline variables was assessed by performing chi-squared tests or Fischers exact test for categorical variables and two-sample Student's *t*-tests for means. Survival curves were calculated by the actuarial life table method, and significance testing based on log-rank tests [4].

Survival was calculated from start of treatment and calculated by the life Table method. Differences between the groups were analyzed by the log rank test [4].

Table 1. Treatment regimes

Awkly –	Adriamycin 20 mg q weekly (max. cum. dose 750 mg/m^2)
VAC –	Vincristine 2 mg Adriamycin 50 mg/m^2 q 3 weeks (max. cum. dose 500 mg/m^2) Cyclophosphamide 600 mg/m^1

RESULTS

All the 128 patients were considered evaluable for response, survival and toxicity. Main patient characteristics are summarized in Tables 2 and 3. One patient had received 5–fluorouracil for treatment of metastases, and 25 had received adjuvant chemotherapy, usually CMF for 1 yr (Table 4). Response rates were 31% for Awkly and 36% for VAC ($P = 0.62$) (Table 5). Among patients that previously had adjuvant CMF for 1 yr 3/8 VAC and 4/17 Awkly patients responded. The percentage difference in response (CR+PR) is 5.7% between VAC and Awkly with 95% confidence limits of ÷ 10.7% and 22.2%. Median duration of complete remissions were 11.3 months (+) for Awkly patients and 8.0 months (+) for VAC patients. For partial remissions, the figures were 5.0 months and 7.0 months respectively (Table 6). There was no significant difference in survival

Table 2. Main patient characteristics

	Awkly	VAC
No. of patients	62	66
Mean age, yr	59	56
Premenopausal	3	3
Postmenopausal	59	63
ER positive (> 10 pmol/g protein)	19	20
ER unknown	39	45
PgR positive (> 10 pmol/g protein)	11	11
PgR unknown	46	48
Disease-free interval (mean, months)	33	29
Time from first metastases until randomization (mean, months)	16	16

Table 3. Number of sites and dominant site of metastases

	Awkly $n = 62$	%	VAC $n = 66$	%
Number of sites				
1	30	48	34	52
2	26	42	27	41
3	6	10	5	8
Dominant site				
Soft tissue	13	21	15	23
Skeletal	19	31	13	20
Visceral	30	48	38	58

Table 4. Previous treatment

	Awkly (n = 62)	VAC (n = 66)
Chemotherapy:		
Adjuvant (CMF 1 yr)	17	8
Advanced disease (5-fluorouracil)	1	0
Hormone therapy: (Tamoxiphen with or without castration)	62	66
Radiotherapy:	6	11

Table 5. Response

	Awkly n = 62		VAC n = 66	
CR	6	31%	8	36%
PR	13		16	
NC	17		27	
PD	26		15	
Total	62		66	

Table 6. Duration of response (months)

	Awkly median	range	VAC median	range
CR	11.5 +	(4–23)	8.0 +	(3–26)
PR	5.0 +	(2–14)	7.0 +	(1–16)

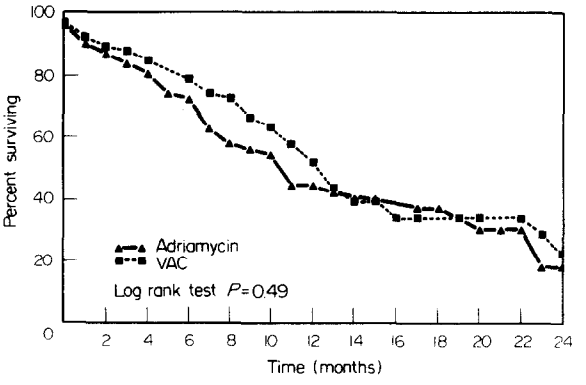

Fig. 1. Life-table plot of survival from start of chemotherapy for the two treatment groups: weekly low-dose Adriamycin (n = 62) *and VAC* (n = 66) *in advanced breast cancer.*

Table 7. Side-effects

	Awkly n = 62	(%)	VAC n = 66	(%)	
None	25	40	1	2	$P < 0.001$
Nausea	21	34	56	85	$P < 0.005$
Vomiting	4	6	43	65	$P < 0.001$
Alopecia	(*4) 5	8	52	79	$P < 0.001$
Bone marrow Depression	6	10	13	20	$P = 0.26$
Neuropathia	0	0	13	16	$P = 0.005$

*Patients with liver metastases

between the two groups whether calculated from start of therapy (Fig. 1) or from time of diagnosis. The response to second line therapy (FuMi) was 20% (56 patients are so far evaluable) with no differences related to primary therapy or response/no response previously. This indicates that FuMi is non-cross-resistant with Awkly/VAC.

Until December 1984, the mean dose of Adriamycin for Awkly patients was 376 mg ranging from 60–1280 mg. For VAC patients the mean dose of Adriamycin was 377 mg with a range of 80–960 mg.

Approximately 40% of Awkly patients had no or negligible side-effects, while almost all VAC patients experienced some degree of toxicity (Table 7). Approximately one third of the patients in the Awkly group experienced some degree of nausea, usually lasting for a few hours after one or more courses. However, vomiting was reported by less than 10% of Awkly patients, in contrast to 65% of VAC patients. Alopecia requiring a wig was seen among less than 10% of Awkly patients as opposed to 80% of VAC patients. Among the five patients in the Awkly group who had alopecia, four had liver metastases.

Pretreatment values of WCC and plt necessitating postponement of a planned course or dose reduction occurred at one course or more for approx. one fifth of VAC patients. Counts of WCC or plt below 1.5 × 10^9/l or 75 c 10^9/l respectively were not seen. Serious infection and secondary bleeding were not reported. Five per cent of Awkly patients had WCC or plt pretreatment values at one course or more below 4.0 × 10^9/l or 125 × 10^9/l. Two patients with liver metastases had at one time WCC on 2.8 and 2.9 × 10^9/l. These were the lowest values recorded. Values of trombocytes below 125 × 10^9/l were not measured. No planned course of Awkly was postponed or reduced due to bone marrow depression.

Clinical evidence of cardiotoxicity was not observed in either group, However, cardiac ejection fraction studies have only been done lately and in a few patients. Electrocardiographic changes that could be ascribed to Adriamycin were not observed.

Neuropathia was not seen among Awkly patients

while paresthesia of hand or feet was seen in 20% of VAC patients.

DISCUSSION

The groups of patients balanced well according to age, disease free interval and time from first metastases to randomization.

There is no significant difference between patients receiving Awkly or VAC in relation to response rate, duration of remission or survival. But the study has little statistical power to detect a small difference in treatment response as shown by the wide confidence interval. The response rate (36%) for VAC is comparable to that recorded in an earlier prospective study from The Norwegian Radium Hospital (35%) [1]. The reason for the relatively low response rate can possibly be attributed to a relatively long interval from first metastases until start of chemotherapy (16 months), comparatively advanced stage of disease and the fact that *all* patients were considered evaluable for response.

Progressive disease was reported more frequently in the Awkly group. This could reflect that a somewhat longer time to objective remission is observed for Awkly patients as compared to VAC. Thirteen out of the 19 remissions in the Awkly group were recorded after more than 3 months on treatment as opposed to 8/24 among VAC patients ($P = 0.03$, Fisher Exact test). Accordingly, in some cases treatment for Awkly patients may have been discontinued too early. This notion is supported by data from an ongoing study where the response rate for Awkly seems to be around 40%.

The main differences between the two regimes is the relative lack of toxicity for the Awkly regime as opposed to the considerable toxicity observed among VAC patients. The most important difference is with regard to nausea, vomiting and alopecia which were observed in almost all VAC patients. In the five cases of Awkly induced alopecia, four had extensive liver metastases, possibly contributing to toxicity. It is also pertinent to point out that one patient not included in this study, and with extensive liver metastases, experienced a WCC drop to $0.9 \times 10^9/l$ on Awkly.

In conclusion, weekly doses of Adriamycin as single agent therapy for advanced breast cancer seem to be as effective as the VAC combination delivered every third week. The side-effects from Awkly are less than following VAC and negligible for most patients. However, patients with liver metastases endure more side-effects than patients with normal liver, and for these patients regular blood counts are advisable also for Awkly therapy.

We would like to emphasize that the Awkly regimen only has been properly evaluated in advanced breast cancer, and should not be employed as a *general* principle in cancer therapy. The therapeutic advantage of weekly Adriamycin remains solely on the improvement in quality of life. This is very important, however, as the present therapeutic aim of treatment of advanced breast cancer is optimal palliation.

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